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Fakulteta za farmacijo

NANČA ČEBRON LIPOVEC

VPLIV FARMACEVTSKIH INTERVENCIJ NA POGOSTNOST NAPAK PRI PREDPISOVANJU, IZDAJI IN DAJANJU ZDRAVIL BOLNIKOM Z NAZOGASTRIČNIMI SONDAMI

IMPACT OF PHARMACIST INTERVENTIONS ON THE FREQUENCY OF MEDICATION ERRORS IN PATIENTS WITH NASOGASTRIC ENTERAL FEEDING TUBES

DIPLOMSKA NALOGA

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Predsednik diplomske komisije: zasl. prof. dr. Aleš Krbavčič

Članica diplomske komisije: doc. dr. Barbara Ostanek

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1 ABSTRACT

In the last decade, the use of enteral feeding has expanded due to its advantages over parenteral nutrition. Medication use in patients with enteral feeding tubes represent a challenge since it often requires changes in drug therapy and formulation. If changes are not implemented, that may result in adverse drug events.

Our prospective randomised control trial compared the frequency of medication errors and preventable adverse drug events in a group of patients with enteral feeding tubes receiving extensive medication review by a research pharmacist, focused on the suitability of drugs for enteral feeding tube administration, and a group of patients with enteral feeding tubes receiving standard practice.

The study included 60 patients with enteral feeding tubes from a teaching hospital in Portugal. Patients were randomised into both groups, their medical documentation was reviewed by the researcher for the data collection and in case of medication errors, suspected adverse drug events were assessed according to probability and severity by an independent pharmacist.

The rate of prescribing errors was 11% and 8% (t-test, $p>0.05$) in the control and intervention group, respectively, and the dispensing error rate was 8% and 4%, respectively ($p<0.05$). In the intervention group, 34 pharmacist interventions were suggested, 111 incorrect doses were administered and resulted in 4 non-doubtful adverse drug events. The high number of incorrect doses administered in the intervention group was a consequence of low pharmacist interventions acceptance rate (76%). However, if all proposed interventions had been accepted, only 19 incorrect doses and 1 non-doubtful ADE would have happened. In the control group, 7 pharmacist interventions were detected, 151 incorrect doses administered causing 8 non-doubtful adverse drug events.

The study showed that patients with enteral feeding tubes are at high risk of medication errors and adverse drug events. Both can be significantly reduced by extensive drug therapy review conducted by pharmacists.

2 RAZŠIRJEN POVZETEK

Uvod: Uravnotežena prehrana je bistvena za življenje. Ko prehranjevanje po naravni poti ni možno, se uvede umetno hranjenje. Poznamo dve vrsti umetnega hranjenja: enteralno, t.j. preko prebavnega sistema, in parenteralno, t.j. preko krvnega obtoka. Enteralno hranjenje ima mnoge prednosti pred parenteralnim, npr.: vnaša se po fiziološki poti, je manj invazivno in manj agresivno, zmanjšuje možnost infekcij, pospešuje bolnikovo okrevanje, omogoča večjo avtonomnost bolnika in nenazadnje predstavlja nižje stroške. Enteralno hranjenje je zato metoda izbora pri vseh bolnikih, ki imajo prebavila delujoča in primerno prehodna. Prehrano se vnaša preko različnih vrst prehanjevalnih sond, ki se razlikujejo po mestu vstopa (nos ali usta) in izstopa (želodec, dvanajstnik, tanko črevo). Za kratkotrajno umetno hranjenje se napogosteje uporablja nazogastrične sonde, t.j. od nosa do želodca, poznamo pa tudi orogastrične sonde, nazoduodenalne (od nosa do dvanajstnika) in nazojejunalne (od nosa do tankega črevesa). Ko pričakujemo, da bo bolnik potreboval umetno hranjenje daljši čas, je priporočljiva uporaba perkutane gastrostomije (PEG), t.j. sonde, vstavljene v želodec preko trebušne stene, saj so takšne sonde najbolj estetske in udobne. Najpogostejši zapleti pri enteralnem hranjenju so aspiracija hrane, zastajanje želodčne vsebine in zamašitev sonde. Čeprav sonde v osnovi niso namenjene dajanju zdravil, je takšna uporaba velikokrat neizogibna. Pri tem je potrebno skrbno izbrati farmacevtsko obliko zdravila in način dajanja. Priporočljiva je izbira tekočih farmacevtskih oblik ali trdnih oblik, ki so lahko topne oz. se smejo raztapljati v vodi. Ko slednje ni možno, je potrebno trdne oblike streti, kar pa pomeni izvenlicenčno uporabo zdravila; proizvajalec v tem primeru ne odgovarja za zaplete ali neželene učinke. Zdravil s podaljšanim sproščanjem ne smemo nikoli streti ali raztapljati, saj to interferira z načinom sproščanja in povroči sprostitev celotnega odmerka naenkrat, kar lahko povzroči toksične krvne koncentracije učinkovine in neželene učinke. Gastrorezistentnih oblik ne smemo treti in dajati po gastričnih sondah, saj stretje uniči gastrorezistentno oblogo, izpostavi učinkovino kislemu želodčnemu mediju in lahko povzroči neučinkovitosti zdravila. Tretje citotoksičnih učinkovin ali hormonov je lahko nevarno za zdravstveno osebje.

Neupoštevanje splošnih priporočil lahko povzroča napake v predpisovanju, izdaji in dajanju zdravil kot tudi neželene dogodke, povezane z zdravil.

Namen: Primerjati pogostnost napak v predpisovanju, izdaji in dajanju zdravil in neželene dogodke, povezane z zdravil, v dveh skupinah bolnikov z nazogastročnimi sondami. V eni skupini je terapija natančno pregledana s strani raziskovalca s poudarkom na primernosti uporabe za bolnike z nazogastričnimi sondami, v drugi skupini pa farmacevt izvaja standardni rutinski pregled terapije.

Materiali in metodologija: Študijo smo izvedli v splošni bolnišnici *Hospital Egas Moniz v* Lizboni na Portugalskem. Bolnišnica ima 400 postelj in zajema vse specializacije, razen porodništva in pediatrije. Zdravila se predpisujejo in izdajajo preko elektronskega predpisovanja in se izdajajo na pacienta. Vsako zdravilo pred izdajo pregleda farmacevt. V študijo so bili vključeni bolniki iz 5 oddelkov: Interna medicina IA in IIA, nevrokirurgija, nevrotravma in oddelek intenzivne nege. Izvedli smo kvantitativno prospektivno randomizirano študijo s 60 bolniki (30 na skupino). V študijo so bili vključeni bolniki, ki so morali imeti predpisano vsaj eno zdravilo za peroralno uporabo, ki je bilo dano po sondi. Kot napako smo šteli vse nepravilnosti v predpisovanju in izdaji zdravil kot posledico dajanja zdravila po sondi. Napake smo razdelili na absolutne, t.j. predpisovanje ali izdaja zdravila s prirejenim sproščanjem, gastrorezistentne oblike ali drugih zdravil, ki se ne smejo nikoli dajati po sondi, ter na relativne napake, t.j. predpisovanje in izdajo zdravil, ki imajo primernejšo farmacevtsko obliko za dajanje po sondi ali pa obstaja primernejša učinkovina v isti terapevtski skupini za tako dajanje. Kot vir informacij smo uporabili angleški in portugalski priročnik za dajanje zdravil po sondi ter povzetke glavnih značilnosti zdravil in navodila za uporabo ocenjevanih zdravil. Neželene dogodke, povezane z zdravili, smo ocenjevali pri bolnikih z absolutnimi napakami v predpisovanju in izdaji. Bolniki so bili porazdeljeni naključno v eno od skupin in nihče razen raziskovalca ni vedel, v katero skupino so vključeni. V intervencijski skupini smo natančno pregledali terapijo bolnikov 24 ur po hospitalizaciji, smo ocenili primernost terapije glede na uporabo zdravil po sondi in farmacevtom, vključeni v intervencijsko skupino, predlagal spremembe. Če so farmacevti soglašali s spremembo, so jo

potrdili preko elektronskega sistema ali pa osebno zdravniku ali medicinski sestri. Terapijo bolnikov smo spremljali vsak delovnik in predlagali potrebne spremembe. Bolnike smo spremljali do odpustitve, premestitve ali dezintubacije oz. največ 10 dni. V kontrolni skupini so farmacevti, ki niso vedeli za potek študije, opravili rutinski pregled terapije in po potrebi predlagali spremembe. 10 dni po vključitvi v kontrolno skupino smo pregledali in ocenili terapijo bolnikov glede na uporabo zdravil po sondi in pregledali intervencije, vnešene v elektronski sistem predpisovanja. Če je bil bolnik še vedno hospitaliziran in intubiran, smo predlagali morebite manjkajoče intervencije. S pomočjo obrazca smo zbrali podatke o številu predpisanih zdravil za peroralno uporabo, številu napak v predpisovanju in izdaji, številu farmacevtskih intervencij in številu bolnikov, ki niso imeli zabeleženega podatka o uporabi sonde v elektronskem sistemu v obeh skupinah. Pri bolniki s prepoznanimi absolutnimi napakami v predpisovanju in izdaji zdravil smo pregledal, ali je bil pričakovani neželeni dogodek, povezan z zdravilom, zabeležen v pacientovi kartoteki, zapisih medicinskih sester in v laboratorijskih izvidih. Verjetnost povezave med neželenim dogodkom in napako v predpisovanju in izdaji (dvomljiva, možna, verjetena, nedvmona) ter resnost neželenega dogodka (blag, zmerno resen, resen, smrten) je ocenil klinični farmacet, ki ni bil vključen v prejšnje faze študije. Zbrane podatke smo statistično analizirali s pomočjo programa SPSS *Statistics* 17.0.

Rezultati: Skupini sta bili primerljivi po porazdelitvi spolov, starosti, porazdelitvi po oddelkih, številu predpisanih zdravil za peroralno uporabo in številu dni opazovanja ($p>0.05$). V kontrolni skupini 13% bolnikov ni imelo zabeleženega podatka o uporabi sonde, v intervencijski skupini pa 37%. Za 14% zdravil, predpisanih v kontrolni skupini, in 20% zdravil, predpisanih v intervencijski skupini, v izbrani literaturi ni bilo podatkov o primernosti uporabe zdravil po sondi. Absolutne napake v predpisovanju smo odkrili v 11% predpisanih zdravil v kontrolni skupini in 8% v intervencijski skupini. V slednji so farmacevti intervenirali v 14 od 15 napak, vendar je bilo zgolj 8 intervencij sprejetih. V kontrolni skupini so farmacevti intervenirali v 5 napakah od 20 in so bile vse sprejete. Zavrnjene intervencije so imele za posledico 15 absolutnih napak v izdaji v kontrolni skupini in 7 absolutnih napak v

intervencijski skupini. Relativne napake v predpisovanju in izdaji so bile pogostejše, 20% v kontrolni skupini in 18% v intervencijski glede na vsa predpisana zdravila za peroralno uporabo; v kontrolni skupini sta bili izvedeni 2 intervenciji, ena je bila sprejeta, v intervencijski pa 20, od tega jih je bilo 66% sprejetih. Relativne napake v izdaji so tako znašale 19% v kontrolni skupini in 11% v intervencijski skupini. Skupno so farmacevti naredili 16 intervencij v kontrolni skupini, od česar je bilo 88% sprejetih, v intervencijski skupini pa 90 intervencij, sprejetih je bilo celokupno 77%. 85% predlaganih intervencij v intervencijski skupini je zajemalo svetovanje o pravilnem vnašanju zdravil, interakcijah, stranskih učinkih, ipd. Absolutne napake v predpisovanju in izdaji zdravil so povzročile dajanje 151 odmerkov zdravil, neprimernih za dajanje po sondi, v kontrolni skupini (0.6 na bolnika na dan opazovanja) in 111 takšnih odmerkov v intervencijski skupini (0.4 na bolnika na dan opazovanja). Če bi bile vse farmacevtske intervencije v intervencijski skupini sprejete, bi se število zmanjšalo na 19 odmerkov zdravil, neprimernih za dajanje po sondi (0.1 na bolnika na dan opazovanja, $p<0.05$). Od 16 domnevnih neželenih dogodkov, povezanih z zdravili, v kontrolni skupini je ocenjevalec ocenil 8 dogodkov kot verjetno, možno ali nedvomno povezanih z napako v predpisovanju, izdaji ali dajanju zdravila (27 na 100 bolnikov), od tega 6 kot »možno« in 2 kot »verjetno«. V intervencijski skupini so bili 4 dogodki od skupno 11 domnevnih neželenih dogodkov ocenjeni kot »verjetno«, »možno« ali »nedvomno« povezani z napako v predpisovanju, izdaji ali dajanju zdravila (13 na 100 bolnikov), od tega 3 kot »možno« in 1 kot »verjetno«. 3 od slednjih so bili posledica nesprejetih farmacevtskih intervencij. Od 8 dogodkov »verjetno« in »možno« povezanih z napako v predpisovanju, izdaji ali dajanju zdravila v kontrolni skupini je bilo 6 ocenjenih kot »zmerno resnih« in 2 kot »resna«, v intervencijski skupini pa 1 kot »blag« in 3 kot »zmerno resni«. Od vseh neželenih dogodkov, »verjetno« ali »možno« povezanih z napako v predpisovanju, izdaji ali dajanju zdravil, je bilo 92% posledica vnašanja farmacevtskih oblik s podaljšanim sproščanjem.

Diskusija: Študija predstavlja prvi poskus ocene neželenih dogodkov, povezanih z zdravili, pri bolnikih z nazogastričnimi sondami. Študija ima nekaj omejitev. Napake smo ocenjevali

glede na izbrano in omejeno literaturo; izbira druge literature bi nas lahko pripeljala do drugačnih rezultatov. Možno je, da je med izvajanjem intervencij prišlo do t.i. kontaminacijskega efekta, to je vpliv intervencij v intervencijski skupini na kontrolno skupino, kar je morda zvišalo število intervencij in zmanjšalo število napak v kontrolni skupini. Podatke o številu intervencij smo zbirali zgolj preko sistema elektronskega predpisovanja, zato je možno, da so bile nekatere spregledane. Neželeni dogodki so bili ocenjeni zgolj kot posledica absolutnih napak in ne tudi relativnih, zato je lahko dejansko število neželenih dogodkov višje. Ocenil jih je samo en ocenjevalec. Vseeno pa rezultati kažejo, da so pacienti s sondami izpostavljeni visokemu številu napak pri ravnavnju z zdravili in visokemu številu neželenih dogodkov, povezanih z zdravili. Število absolutnih napak v predpisovanju je primerljivo z napakami v predpisovanju v pediatrični populaciji, ki velja za eno najbolj izpostavljenih tovrstnim napakam (25). Relativne napake v predpisovanju so še pogostejše in primerljive s prejšnjimi študijami na tej populaciji (18). Farmacevti med rutinskm pregledom terapije niso uspeli odkriti vseh napak v predpisovanju, verjetno zaradi pomanjkanja časa in preobremenjenosti (29). Absolutne napake v predpisovanju in izdaji so povzročile dejanske neželene dogodke različnih stopenj resnosti, njihova pogostnost pa je bistveno višja od poročanega povprečja (27). Velika večina neželenih dogodkov je bilo posledica dajanja farmacevtskih oblik s podaljšanim sproščanjem, kar potrjuje nevarnost tretja tovrstnih farmacevtskih oblik. Odstotek sprejetih intervencij v intervencijski skupini je bil nižji od povprečja (30,31). Če bi bile vse intervencije v intervencijski skupini sprejete, bi to signifikantno znižalo število odmerkov zdravil, neprimernih za dajanje po sondi, in posledično število neželenih dogodkov, povezanih z zdravili.

Zaključki: Bolniki, ki prejemajo zdravila po nazogastrični sondi, so izpostavljeni visokemu številu napak v v predpisovanju, izdaji in dajanju zdravil in neželenim dogodkom, povezanih z zdravili. Farmacevti lahko z natančnim pregledom terapije preprečijo večino napak in neželenih dogodkov, vendar je sprejemanje njihovih intervencij nizko.

3 ABBREVIATIONS

ADE – Adverse Drug Event

ADME – Absorption Distribution Metabolism Excretion

ADR – Adverse Drug Reaction

EFT – Enteral Feeding Tube

GI - Gastrointestinal

GIT – Gastrointestinal Tract

GR – Gastro-Resistant

ICU – Intensive Care Unit

IV - Intravenous

ME – Medication Error

Med IA – Internal Medicine IA

Med IIA – Internal Medicine IIA

PIL – Patient Information Leaflet

PR – Prolonged-release

RCT – Randomised Control Trial

SmPC – Summary of Product Characteristics

TDM – Therapeutic Drug Monitoring

4 INTRODUCTION

In the first part of this chapter we introduce the term enteral nutrition, its uses, types and advantages, present types of enteral feeding tubes (EFTs) and overview different oral medication formulations, the possibility and methods of their administration via EFT. The second part defines medication errors (MEs), adverse drug events (ADEs) and their correlation, and briefly presents published studies on MEs in patients with EFT.

4.1 ENTERAL NUTRITION

CLASSIFICATION AND ADVANTAGES

In order to maintain life and health it is necessary to have a correct and equilibrated alimentation. In some circumstances, an adequate alimentation cannot be achieved by the ordinary routes. Patients may not be able to ingest, digest or absorb an adeqate quantity of nutrients from food. In such cases, artificial nutrition is used.

There are two types of artificial nutrition:

- enteral nutrition where the nutrtients are administered through the digestive system,
- parenteral nutrition where the nutritients are administered through the circulatory system.

Enteral nutrition has various advantages over parenteral nutrition. The use of the physiological route for the administration of nutritients is generally encouraged as well as it makes it easyer to correct the patient's nutritional state. Moreover, it is less agressive and less invasive than parenteral nutrition and the frequency of infections, which are common with the latter, is lower. Enteral nutrition also helps to maintain the gastrointestinal (GI) mucosa structure and function, many times preventing atrophy and bacterial translocation, which is the passage of GI bacteria to the lymphatics or visceral circulation. Furthermore, it allows higher autonomy

of the patient, which has a positive impact on the patient's psychological state. Moreover, it can be used domicilary and the costs are lower (1). Therefore, the use of enteral nutrition over parenteral is suggested whenever (a) the patient has adequate capacity of GI absorption, (b) there is no contraindication for the use of the GI tract and (c) access can be safely obtained (2).

INDICATIONS FOR THE USE OF ENTERAL NUTRITION

In general, nutrition support is indicated for patients previously well-nourished, who have been or will be without oral intake for 5 to 10 days. In case of malnourished patients, nutrition should start early on, depending on the level of inappropriateness of their diet (2). The use of enteral nutrition covers a wide range of clinical conditions and age groups. However, the most common being cerebrovascular accident and cancer patients (3).

ENTERAL FORMULAS

Enteral formulas may be specialized or unspecialized. Unspecialized formulas cover general nutrition needs, but can vary in the content of proteins, fats, fibers, etc. Specialized formulas are adopted to the specific needs of the clinical conditions of patients. These conditions include hepatic failure, renal failure, pulmonary disease, metabolic stress, immunomodulation, glycaemic control, etc.

The enteral formula can be administered to a patient continuously (continuous feeding) or during determined periods in the day (intermittent feeding). (2)

4.2 ENTERAL FEEDING TUBES

Feeding tubes represent an alternative for nutrition when oral intake is inadequate or inadvisable. They are used in primary and secondary care.

TYPES OF ENTERAL FEEDING TUBES

There are various types of enteral feeding tubes that differ in size, length, site of insertion and exit. The diameter of EFT is normally expressed in French units (1 French unit = 0.33 mm) and divides EFT in small-bore (e.g. 5-12 French) and large-bore (≥14 French) tubes. However, the main classification is typically based on the site of insertion (nasal, oral, percutaneous) and exit (stomach, duodenum, jejunum). Thus the main types include nasogastric EFT, orogastric EFT, nasoduodenal EFT, nasojejunal EFT, percutaneous gastrostomy, percutaneous jejunostomy and percutaneous gastrojejunostomy. The type of EFT chosen for a patient depends on several factors, e.g. intended duration of intubation, concurrent diseases or injuries and the risk of impaired gastric motility or aspiration. Nasoenteric tubes are prefered for short-term intubation, while percutaneous tubes are mainly used for long-term intubation. The optimal site of exit of EFT is the stomach since is generally more convenient, less costly and easier to access. (1,2)

Figure 1 shows sites of insertion and exit of different EFT. Table 1 summarises their general characteristics, advantages and disadvantages.

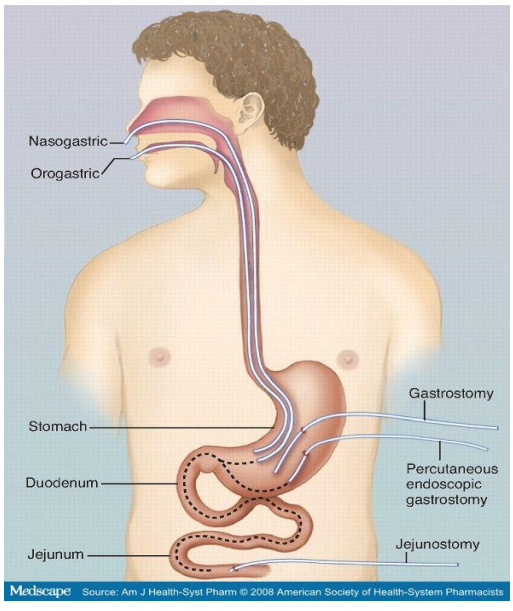

Figure 1 Sites of insertion and exit of EFT (1)

Table I General characteristics, advantages and disadvantages of different types of EFTs (4)

EFT TYPE	GENERAL CHARACTERISTICS	ADVANTAGES	DISADVANTAGES
Nasogastric tubes	Most widely used. First option for short-term feeding. Small-bore tubes are used for feeding while large-bore serve primarily for aspiration.	Use of natural route of administration of food Antimicrobial effect of gastric acid Allows intermittent feeding convenient, less costly, easy to place	Unaesthetic and uncomfortable Contraindicated in high risk of bronchoaspiration or gastroesophagic reflux
Orogastric tubes	Used when application of nasogastric tubes is not possible (sinusitis, head injury, premature infants, etc.)	Same as nasogastric tubes	Same as nasogastric tubes
Nasoduodenal tubes	Used for short-term feeding in sedated or coma patients with high risk of aspiration, retarded gastric emptying, anorexia nervosa.	Minimal risk of aspiration, reflux or desintubation Allows feeding directly before and after gastric surgery	Not convenient for long-term feeding Unaesthetic and uncomfortable Difficult to apply and keep correctly positioned
Nasojejunal tubes	Used similarly as nasoduodenal tubes. Used for drug administration only in exceptional circumstances.	Same as nasoduodenal tubes.	High tendency to displace High likelihood of tube occlusion
Percutaneous gastrostomy (PEG)	Most widely used in long-term feeding, in patients with swallowing difficulties (neurological problems, head, neck or ORL cancer)	Can be placed under conscious sedation Comfortable and aesthetic Minimized risk of regurgitation, aspiration or desintubation	Contraindicated in patients with massive ascites, high digestive fistulas, peritoneal dialysis, obesity, coagulation disorders
Percutaneous jejunostomy (PEJ)	Used in long-term feeding in patients with high risk of aspiration or with non-functioning GIT above the jejunum	Comfortable, aesthetic and well tolerated Suitable for immediate post-operational feeding	Contraindicated in complete intestinal obstruction, massive ascites, peritoneal dialysis Displacement can lead to peritonitis

ENTERAL FEEDING TUBE OCCLUSION

The main complications with enteral nutrition and use of EFT are pulmonary aspiration of the enteral formula, gastric residual volume and tube occlusion. Although research studies give conflicting data on the reasons and frequency of the first two complications, the tube occlusion is one of the most common problems in enteral nutrition administration. (5) The possible reasons for EFT occlusion include:

- feed precipitate from contact with an acidic fluid,
- stagnant feed in the tube,
- contaminated feed,
- intermittent feeding,
  incorrect drug administration,
- feeding tube properties.

Although the feed is considered the most common cause of occlusion, use of inappropriate medication formulation increases the risk. Particles from inadequately crushed tablets may result in occlusion as well as interactions between medication and feed or two incompatible medications. Routinely flushing the tube with 15 to 30 ml of water after each intermittent feeding and before and after adminstration of medication is proved to be the most effective method for occlusion prevention. Otherwise, EFT can be unblocked with the help of liquid irrigants, pancreatic enzymes or mechanical devices; if all these methods are unsuccessful, the tubes need to be replaced, which can result in loss of feed, increased risk of morbidity and has financial implications (3).

4.3 MEDICATION ADMINISTRATION VIA EFT

Enteral feeding tubes are primarily designed for nutrition and not for administration of drugs. When use of medications through EFT is unavoidable, general recommendations should be followed to assure therapy efficacy and safety for the patient.

4.3.1 GENERAL CONSIDERATIONS

The main restrictions represent the tube type and placement, type of feeding and type of medication administered.

Narrow tubes and long tubes are prone to obstruction, therefore medication administration through these tubes should be avoided. Special caution should be taken when using jejunostomy EFT. Oral medications are designed to be administered through the mouth and to pass the stomach. Many need the acidic pH of the stomach to achieve adequate solubilty of the active substance and effective absorbtion. The stomach can be the site of absorbtion or site of action of medications. Administering such medications through jejunostomy tubes can decrease their effectiveness. The ADME characteristics of the medication should thus be investigated before administration via jejunostomy tubes. On the other hand, enteric-coated medications can only be administered through these tubes. The enteric coating is designed to protect the active substance against acidic pH and to desintegrate in the small intestine. Since crushing and administration via gastric tubes can interact with the coating and reduce the effectiveness of the medication and also cause irritation of the gastric mucosa, GR medications should not be crushed and administered through gastric tubes.

Medications should never be mixed with the enteral feed. When a patient is receiving continuous enteral feeding, the first consideration is potential interaction with the medication. The interaction depends both on the feed type and on the medication. The problem of interaction may lay in the compatibility of the feed and medications or stability of one or the other (5). This can result in EFT obstruction, changes in drug or nutrient delivery and bioavailability, as well as changes in GIT function. The most studied interactions include carbamazepin, warfarin, phenytoin, fluconazole and levofloxacin. (6) If administration of the medication requires feed discontinuation, it should be closely monitored to assure adequate nutrition delivery. Handbooks should be consulted for detailed information.

4.3.2 BEFORE ADMINISTRATION

The medication therapy of every patient with EFT should be reviewed and the number of medications reduced to the minumum possible. Medications that are not immediately necessary should be discontinued (e.g., statins or hormone replacement therapy). The remaining medications should be attempted to be exchanged for an alternative, non-oral route. However, this decision should be assessed against the clinical condition of the patients and the practical limitations. Only a limited number of medications are available as transdermal systems. Sublingual and buccal formulations cannot be used in patients with mouth injuries, decreased mental status, vomiting or excessive salivation. Formulations like injections may be practical for hospital care, but have limited applicability in the domicilarly setting. When an alternative route of administration is not available, oral medications should be switched to a medication type and formulation that reduces the dosage interval. (3,5,6)

4.3.3 CHOICE OF FORMULATION

If alternative routes are not available or are inadequate, medications have to be given through EFT.

LIQUID PREPARATIONS

ORAL SOLUTIONS

The preferred choice of formulation are solutions and soluble tablets, since these are readily absorbed in the GIT and do not cause tube occlusion. Oral solutions may have a different concentration than solid formulations or may be registered for paediatric use. Changes in strength require alteration of the daily dose and the frequency of administration. Paediatric solutions may additionally require administration of large volumes of liquid, which may cause intolerability.

Solutions, especially when administered in large amounts, can be a cause of adverse events due to their excipients. Commonly, solutions contain sorbitol as a sweetening agent, which can in daily amounts, higher than 20g, cause GI intolerance, cramping and diarrhea (7). This should be taken into account when a patient may be administered different oral

solutions containing sorbitol. Unfortunately, sorbitol content is not always reported on the labels, SmPCs or PILs of the medicines. Other hypertonic solutions may also cause intolerance when administered to the small intestine. Dilution with 15 to 30 ml of water can reduce irritability and intolerance.

SUSPENSIONS

Suspensions are a preferrable choice, since the sorbitol content is normally lower and the stability of medications is higher. Caution should be taken with granular suspension, since the granules can be too large and or suspension too viscous to be used in EFT.

SOLID FORMULATIONS

SOLUBLE AND DISPERSIBLE TABLETS

These tablets both dissolve or disintegrate when placed in water. Generally, all soluble tablets can be given via EFT, while some dispersible tablets may be made of granules which can cause tube occlusion. These are low cost formulations.

EFFERVESCENT TABLETS

These tablets are made to be dissolved or disintegrated in water, and therefore are appropriate for administration via EFT. However, caution should be taken in giving enough time for full dissolution or disintegration in order to avoid gass production in the tube. The sodium content should be taken into consideration since it tends to be high in this kind of formulation. Use of effervescent tablets may not be appropriate in patients with fluid restrictions.

SUBLINGUAL TABLETS

Although these tablets should not be administered via EFT, they represent a useful alternative route of administration. The patient's ability to produce enough saliva should be considered. Since they are absorbed by the sublingual mucosa, the swallowing ability does not represent an issue.

COMPRESSED TABLETS

Compressed tablets may or may not dissintegrate when placed into water, depending on the excipients used. Dispersion in water should always be attempted before resorting to crushing due to its legal and health considerations (see Limitations in crushing medications). An alternative formulation is preferable.

PROLONGED-RELEASE TABLETS

Prolonged-release tablets are designed to release the active substance through a definite period of time. Dissolving or crushing the tablet interferes with the modified release and transform the formulation in immediate-release. This can cause dose-dumping and consequently toxic serum levels, followed by a period of ineffectiveness. Thus, this kind of medications formulations should never be administered via EFT.

GASTRO-RESISTANT TABLETS

The enteric coating of gastro-resistant tablets protects the active substance(s) from coming into contact with the gastric acidic medium. Destroying the coating whether by dissolving or crushing the tablet will affect the effectiveness of the medication, might cause irritation of the GIT and EFT occlusion. These formulations should therefore never be administered via gastric EFT, but can be used in tubes ending in the jejunum or lower.

HARD GELATIN CAPSULES

In general, these capsules may be opened, the content mixed with water and administered via EFT. In practice however, their use is limited due to difficulties in opening the capsules, possibility of exposure and limited solubility of the powder.

SOFT GELATIN CAPSULES

In general, soft gelatin capsules are not recommended for use via EFT. Although the capsules can be pierced and the content mixed with water, the medications are normally poorly soluble in water and the administration of the total amount of medication cannot be assured. Switch to an alternative formulation is recommended. (8)

Table II Summary of recommendations on use of oral medication formulations via EFT

Formulation	Recommendation
Soluble and dispersible tablets	Can be used via EFT
Effervescent tablets	Generally can be used via EFT
Sublingual tablets	Can be used as an alternative route of administration
Compressed tablets	Limited EFT use, consider alternative formulations
Prolonged-release tablets	Should never be used via EFT
Gastro-resistant tablets	Should never be used via gastric EFT
Hard gelatin capsules	Limited EFT use, consider alternative formulations
Soft gelatin capsules	Limited EFT use, consider alternative formulations

4.3.4 MEDICATION ADMINISTRATION METHODS

In order to avoid interactions with feed or between different drugs and tube occlusion, the tube should be flushed with 15-30 ml of water before and after administration of each drug. If the drug administered is a viscous liquid, it should be diluted with water in equal proportions to avoid tube occlusion. All soluble formulations should be placed into 10 ml of water and allowed to dissolve. To assure that the whole dose is administered, drugs should be dissolved inside the syringe and administered and flushed again with water.

Crushing a tablet can be achieved by using a mortar and pestle or a crushing syringe. The latter is advised for cytotoxic drugs, hormones and antibiotics to protect healthcare professionals from drug exposure and sensitisation. Use of the crushing syringe assures administration of the whole dose of the drug and is less time consuming than use of morat and pestle. Each drug should always be crushed and administered separately. (3)

4.3.5 LIMITATIONS IN CRUSHING MEDICATIONS

As already mentioned, crushing PR formulations will result in dose-dumping and toxic serum levels, followed by drug subtherapeutic levels. GR formulations can result in reduced effectiveness or occluded tube if crushed. Both can cause adverse drug events (ADE).

Besides potential harm for the patient, health and safety of the person crushing and administering it has to be taken into account. Medications like antibiotics, hormones, cytotoxics and immunosupressants can cause unwanted reactions when put into contact with the skin or inhaled. Such drugs should be crushed in a closed container to avoid exposure. If this is not possible, the medication should not be crushed and an alternative formulation has to be considered.

Moreover, crushing a medication alters its formulation and results in unlicensed use. If administration of such medication causes harm to the patient, the manufacturer is no longer responsible for any clinical outcome since the administration of the medication did not follow its marketing authorisation. Therefore, the responsibility falls on the healthcare workers. From this point of view crushing should be avoided at all times. If crushing is unavoidable, the prescriber and pharmacist, responsible for dispensing the medication, should be informed and asked for consent. When possible, the patient should also be asked for approval (8).

4.4 MEDICATION ERRORS AND ADVERSE DRUG EVENTS

4.4.1 DEFINITIONS AND CORRELATIONS

A medication error (ME) is defined as "any error in the prescribing, dispensing, or administration of a drug, irrespective of whether such errors lead to adverse consequences or not" (9). An adverse drug events (ADE) is defined as »Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment" (10). ADEs can be categorized as actual or potential, preventable or non-preventable, ameliorable or non-ameliorable. Adverse drug reactions (ADRs) are ADEs that are not a consequence of medication errors. The correlations between these categories of ADEs and MEs are shown in Figure 2. (11)

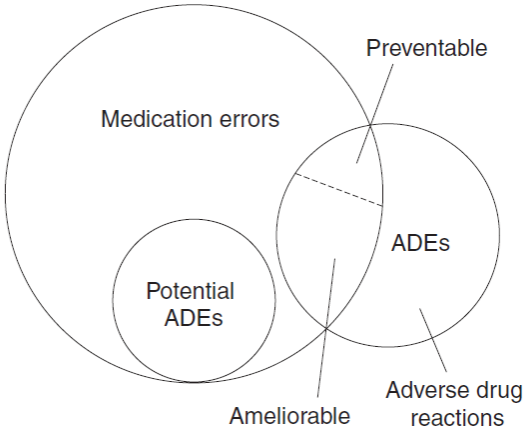

Figure 2 Relationship between adverse drug events (ADEs), potential ADEs and medication errors (resumed by Morimoto)

As can be observed from Figure 2, some MEs result in ADEs while others do not. A potential ADE is a ME with the potential to cause harm, but which does not cause actual harm, for example because the error is corrected before it reached the patient. A common situation in patients with EFT is when a patient is prescribed a PR formulation (prescribing medication error), however, the error is corrected by the pharmacist during prescription validation: the drug is not dispensed nor administered and the error does not reach the patient. A preventable ADE is »an injury that is the result of an error at any stage in the medication use«. In the case of EFT, administration of PR or GR formulations can cause preventable ADE. Amelirable ADE cannot be prevented, but can be reduced if correct action is taken soon enough.

ADEs are usually assessed according to probability and severity. The probability evaluation assesses the causal relationship between the ADE and the drug investigated. The most widely used tool for probability evaluation is the Naranjo algorithm (12). It is composed of 10 questions on the characteristics of the ADE: when the ADE started, whether it has alternative causes, if it stopped when the drug was discontinued and whether it reappeared when the drug was readmistered, etc. Each answer (yes, no, do not know) has a predetermined score (-1, 0, +1, +2); the total score of 10 questions is then divided into

categories of probability (0 = doubtful ADE, 1-4 = possible ADE, 5-8 = probable ADE, > 9 definite ADE) (12). (Attachment 1)

Various scales exist for determining the severity of ADEs, however the most used is the Karch-Lasagna scale (13). It divides severity into 4 categories: mild, moderate, severe and lethal ADEs. In order to make the assessment objective, each category is annexed with a brief description on the impact of and actions that need to be taken to overcome ADEs of this severity. (Attachments 2)

4.4.2 MEDICATION ERRORS AND ADVERSE DRUG EVENTS IN PATIENTS WITH EFT

Drug use in patients with EFTs is prone for the occurance of medication errors, thus special caution is required when prescribing, dispensing and administering drugs in this patient population. If the healthcare team fails to follow recommendations on correct use of drugs via EFT, this can lead to MEs and ADEs.

Various studies that attempted to assess drug use in patients with EFT were conducted. Since administration of drugs to patients with EFT requires special procedures, administration errors are frequent and thus many researchers focused on this error type. The reported rate of administration errors varies from 25.4% (14) to 64.5% (15) and up to 76% (16). Complications in medication administration through EFT, which are not caused by administration errors, were also assessed: the frequency of tube occlusion (16) (17) or the frequency of tube replacements (18). Researchers were also interested in the number of drugs and types of drug formulations used in patients with EFT (18) and the impact of interventions including training nurses, labelling drugs with »do not crush« stickers and setting up a database on oral dosage forms, in diminuishing administration errors (16). Many studies focused on complications of EFT use that relate to enteral nutrition and not to the use of medications through EFT.

However, no studies that assessed the frequency of prescribing and dispensing MEs in relation to the administration of the drugs through EFT, and the resulting ADEs were found.

5 AIMS AND OBJECTIVES

5.1 STUDY AIM

Comparison of the frequency of medication errors and preventable adverse drug events in a group of patients with EFT receiving extensive medication review, focused on the suitability of drugs for EFT administration, and a group of patients with EFT receiving standard medication review.

5.2 STUDY OBJECTIVES

Primary outcomes:

- Number of absolute prescribing and dispensing errors,
- number of incorrect doses administered,
- number of suspected preventable ADE.

Secondary outcomes:

- number of relative prescribing errors,
- number of relative dispensing errors,
- number of suggested and accepted pharmacists' interventions,
- number of medications lacking data on the use via EFT,
- number of patients with non-reported EFT.

6 MATERIALS AND METHODS

6.1 MATERIALS

6.1.1 THE HOSPITAL

The study was conducted in the general hospital *Hospital Egas Moniz (HEM)*, in Lisbon, Portugal. HEM is a 400 bed hospital, which covers all specialties with the exception of pediatrics and obstetrics. In 2005, HEM has become part of the East Lisbon Hospital Center (Centro Hospitalar se Lisboa Ocidental - CHLO), a merging of the 3 main general hospitals of Lisbon, which comprises 900 beds and covers all clinical specialties.

All three CHLO hospitals use a Computerized Physician Order Entry System (CPOE), which includes electronic medical files, electronic nurse notes, electronic laboratory results as well as electronic prescribing.

6.1.2 WARDS

Included in the study were patients from five different wards: the combined ward of neurotrauma (NT), and neurosurgery (NS), the polyvalent intensive care unit (ICU), the internal medicine I ward (Med IA) and the internal medicine II ward (Med IIA). These wards were selected due to the highest frequency of patients with EFT. The data on ward capacity and number of assigned healthcare professionals are summarized below (Table 3).

Table III Capacity and number of healthcare workers in selected wards

	Med IA	Med IIA	NS and NT	ICU*
Number of beds	36	36	26 + 21	11
Number of physicians	28	28	17	9*
Number of nurses	32	30	27 + 17	5*
Number of pharmacists	1	1	1	1

*fixed staff (other healthcare members are scheduled by shifts)

Pharmacists are not fully employed as ward pharmacists, but visits on wards and attendance at ward rounds are part of their duties besides the work in the pharmacy.

6.1.3 PHARMACISTS

The HEM pharmacy employs 10 pharmacists, of whom one is an intern, 9 technicians, 3 administrative personnel and 6 are auxiliary personnel. Every weekday, one pharmacist, one auxiliary and two technicians are present during the afternoon shift (10.30/11.30 until 19.00), while the rest of the team is on morning shift (8.30 until 16.00/17.00). During weekends and on holidays, one pharmacist, two technicians and 1 auxiliary member work from 8.30 to 19.00.

The most visible activity of the pharmacist is the validation of the prescriptions. Most wards have a "daily unit dose" distribution, which means medications are dispensed per patient every day in doses for the next 24 hours. The pharmacist responsible for the direct support to each ward must interpret and validate the prescription, including counseling on drug discontinuation or supplementation, dosage regimen and formulation selection. The validation is done through the electronic prescribing system. When a new medication is prescribed, the pharmacist is notified through the system and the prescription will be validated and the validated order passed electronically to the pharmacy technicians, who are in charge of dispensing the medications. Every prescription is therefore validated by the pharmacist before being dispensed to the ward.

This electronic prescribing system provides basic information about the patient age, gender, weight, previous diagnoses, the type of diet and use of EFT, while also detailed information on the patient's clinical history and momentary status are available. Since physicians use non-proprietary medication names in prescriptions, the system enables the pharmacist to suggest dispensing of a specific brand of medication. The validated prescriptions are visible to ward nurses, thus pharmacists can also include information on the method and the correct time of drug administration and indicate possible interactions.

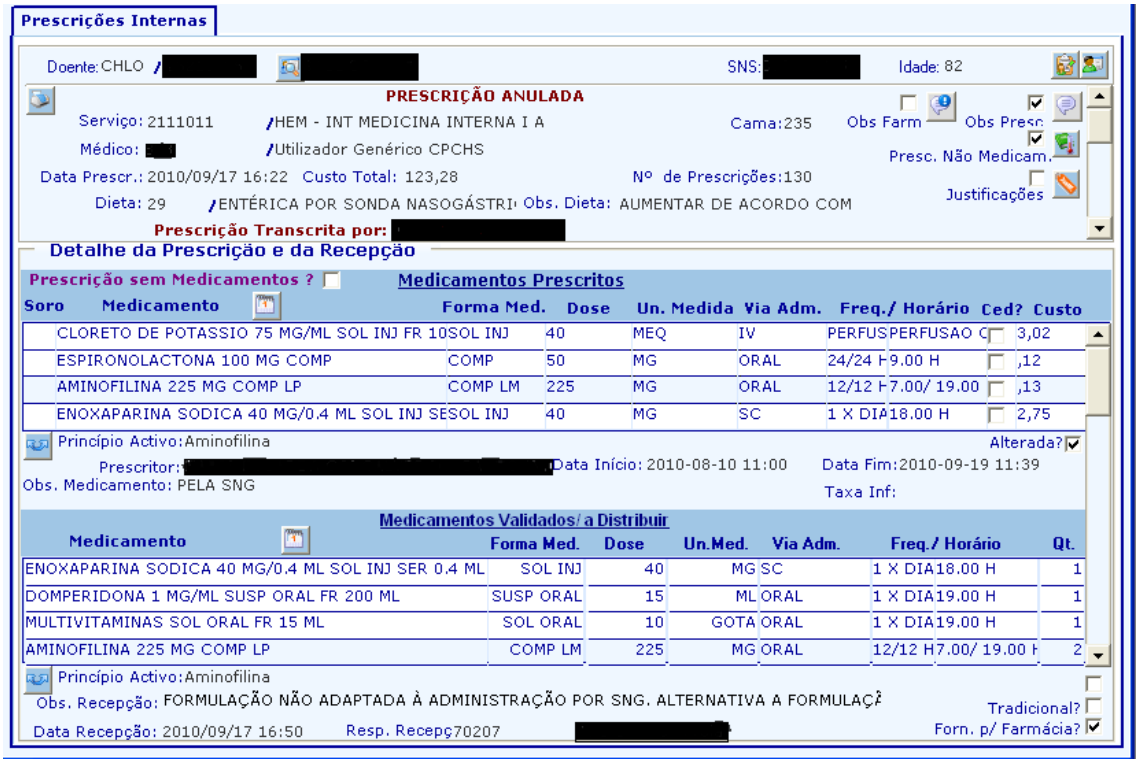

Figure 3 Example of electronic prescribing system (CPOE) used in the hospital – patient history menu.

Besides the work in the pharmacy, pharmacists also regularly visit wards. Each ward has a main pharmacist, who is in charge of the medication therapy of all patients present within that ward. When the main pharmacist is not present at work (e.g., holidays), a backup pharmacist takes over his work, according to a replacement scale among the staff. The main pharmacist participates in the ward-round on average 3 times per week. Besides ward rounds, the pharmacist regularly visits the ward to solve medication-related problems in collaboration with the healthcare team. In average, these pharmacists spend at least 1-2 hours per week day on their ward.

6.2 DEFINITIONS

6.2.1 MEDICATION ERRORS

The most general definition of medication error is "any error in the prescribing, dispensing, or administration of a drug, irrespective of whether such errors lead to adverse

consequences or not" (9). However, since for this study medication errors were solely related to patients with EFT, the definition was narrowed. Thus, an error was defined as "any discrepancy in prescribing or dispensing of a drug due to administration via EFT, irrespective of whether such discrepancies lead to adverse consequences or not".

Since it was not possible to observe nurses during the administration of medications through EFT, this type of MEs was not included in the study.

Thus medication errors were organized in the following categories:

- Absolute prescribing error: Prescribing a prolonged-release or gastro-resistant formulation or other medications that should never be used via EFT according to selected literature.
- Absolute dispensing errors: dispensing a prolonged-release or gastro-resistant formulation or other medications that should never be used via EFT according to selected literature.
- Relative prescribing error: prescribing an oral crushable solid formulation when a non-oral or liquid oral formulation exists or prescribing a medication which has a more appropriate alternative in the same therapeutic group for administration via EFT.
- Relative dispensing errors: dispensing an oral crushable solid formulation when a non-oral or liquid oral formulation exists or dispensing a medication which has a more appropriate alternative in the same therapeutic group for administration via EFT.

6.2.2 PREVENTABLE ADVERSE DRUG EVENTS

Since all suspected ADEs are the consequence of a prescribing or dispensing ME, all ADEs are categorized as preventable (see Introduction). Morimoto defines a preventable ADE as »an injury that is the result of an error at any stage in the medication use« (11). All preventable ADE are therefore medication errors, but not all medication errors result in preventable ADE. This is also true for the presented definition of medication errors in this

study. Some MEs, absolute or relative, are thought to carry a low probability to result in ADE; e.g. dispensing a crushable solid formulation when a liquid alternative is available is a ME because it does not follow the guidelines for correct use of medications via EFT, but it will probably not result in harm to the patient. On the other hand, most absolute MEs are highly likely to result in ADE, e.g. administering a Prolonged-release formulation by crushing will cause dose-dumping and increased drug serum levels, which can potentially harm the patient.

Table IV Correlation between the types of ME and the probability of ADE

<table>
<tr><th></th><th>High probability of ADE</th><th>Low probability of ADE</th></tr>
<tr><td rowspan="2">Medication error</td><td rowspan="2">Prescribing and dispensing a PR or GR formulation or another medication that should never be applied through EFT*</td><td>Prescribing and dispensing a medication which has a more appropriate alternative for administration via EFT in the same therapeutic group</td></tr>
<tr><td>Prescribing and dispensing an oral crushable solid formulation when a non-oral or liquid formulation exists</td></tr>
</table>

*Medications which should never be crushed due to the possibility of contact sensitization of the healthcare team are not included.

According to Marimoto, an ADE that is the consequence of a ME is a preventable ADE. Thus, prescribing and dispensing a PR or GR formulation or other medication that should never be used via EFT is a preventable ADE. Although it is possible that a preventable ADE would be manifested also in the rest of MEs, due to time and human resources restraints, it was decided to assess only the most probable preventable ADE.

6.3 DESIGN

A quantitative, prospective randomized control trial was conducted assessing the frequency of medication errors, incorrect doses administered and preventable adverse drug events due

to incorrect prescribing and dispensing of medications to patients with EFT in a group of patients receiving an extensive medication review, focused on the suitability of drugs for EFT administration, versus a group of patients receiving standard drug therapy check.

Approval of the HEM Ethics Committee was obtained beforehand.

6.3.1 PATIENT INCLUSION AND EXCLUSION CRITERIA

The patients were included if they fulfilled the following criteria:

- medication administration through EFT,
- being prescribed at least one oral medication.

Patients were excluded from the study whenever they were hospitalized and intubated in the selected wards for less than 3 consecutive days. This criterion has been added to assure that the patient is followed long enough to make the assessment of preventable ADEs possible.

6.3.2 INTERVENTIONS

Every hospitalized patient fulfilling the inclusion criteria was assigned a number according to a predetermined randomization plan and included in either the control or the intervention group. Except for the researcher, everybody else involved in the study was blinded for patient group assignment.

CONTROL GROUP

Patients in the control group underwent routine drug therapy check and were reviewed by the researcher only after 10 days. Their drug therapy was reviewed by pharmacists as part of the routine drug therapy check and changes were proposed; these interventions and their realizations were recorded in the electronic prescribing system. Pharmacists could consult the same literature on medication through EFT as the researcher. The patient's drug therapy and pharmacist interventions were reviewed by the researcher only after 10 days of inclusion. If at that time the patient was still hospitalized and intubated, the researcher

assessed the patient's drug therapy against the selected literature and suggested further interventions if needed.

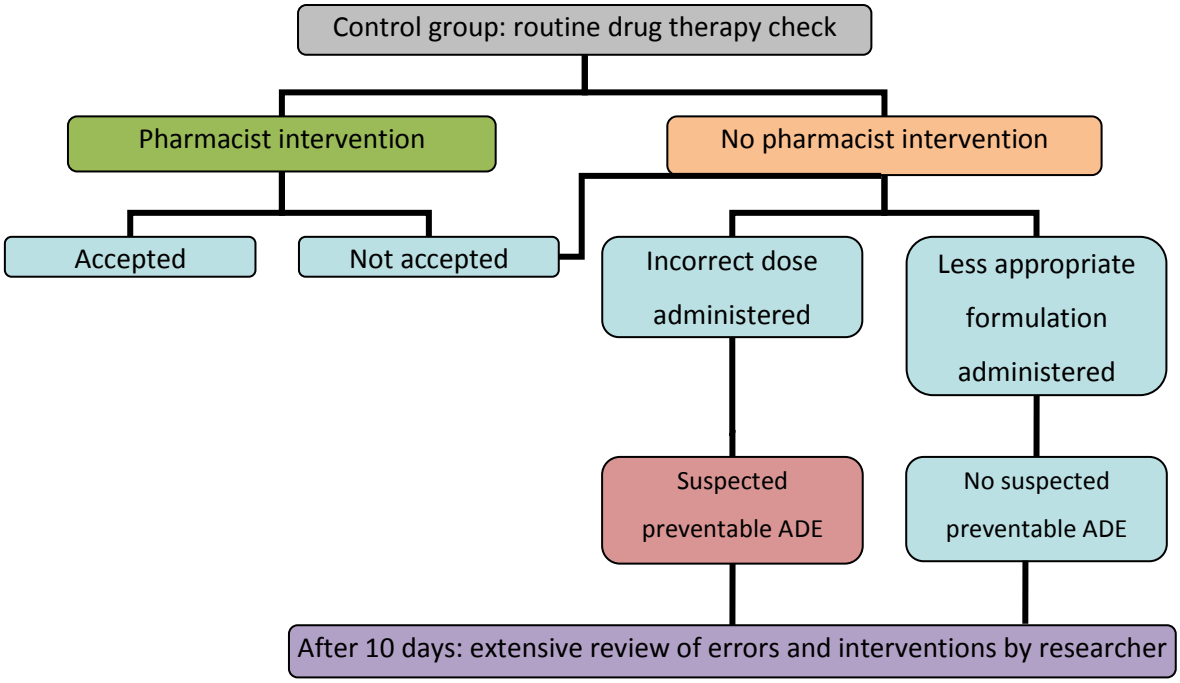

Figure 4 Interventions in the control group

INTERVENTION GROUP

In the intervention group, the patients drug therapy was reviewed by the researcher 24 hours after hospitalization in order to allow standard clinical practice to occur, or on the first working day after hospitalization, in case the patient was hospitalised during the weekend. The researcher reviewed the prescribed and dispensed medications, assessed their suitability for EFT administration against the selected literature and suggested necessary changes to the ward pharmacist. Pharmacists reviewed the researcher's recommended changes and, if they agreed with them, made the interventions required. If the pharmacists did not concord with the suggested changes, the difference in opinion was discussed between the ward pharmacist and the researcher and agreement reached. The interventions were done through the hospital's electronic prescribing system and additional information was conveyed to the physicians and/or nurses orally, by phone or personally on the wards. The drug therapy of the patients was followed daily by the researcher and the

same procedure was used for every medication which needed an intervention. The patients were followed until extubation, discharge or transfer or for maximum 10 hospitalization days, whichever came first.

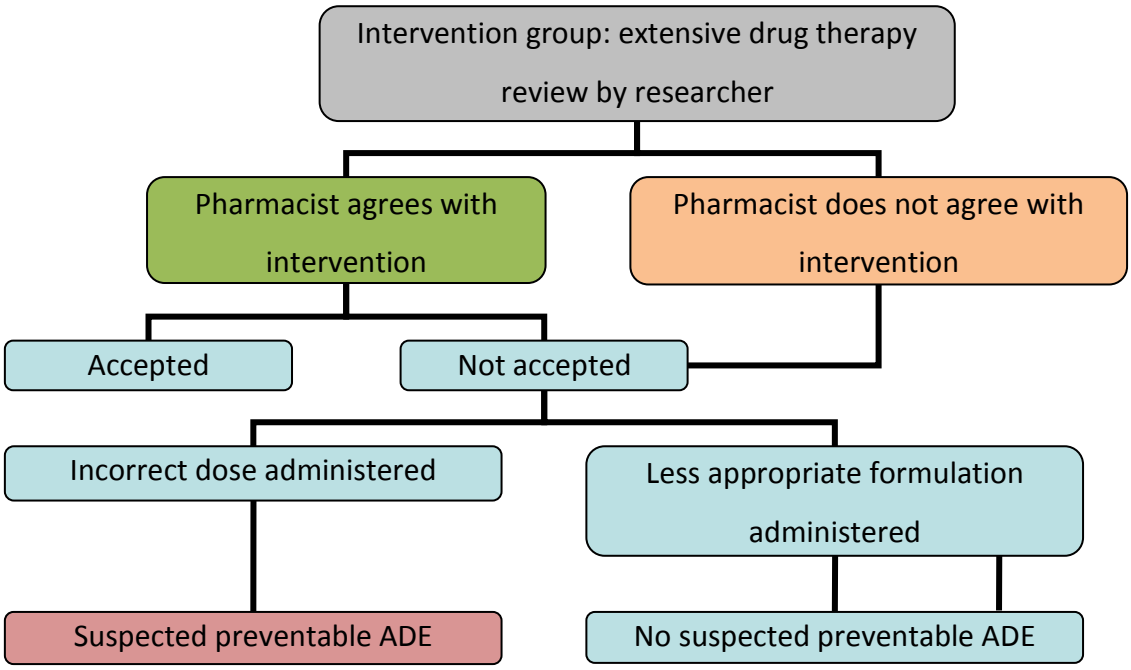

Figure 5 Interventions in the intervention group

6.3.3 SOURCES OF INFORMATION

Various handbooks and guidelines for the administration of medications via EFT exist, which differ in depth and amount of information provided. All the information sources encountered were either local, being developed for the needs of a specific hospital, or national. This is mainly due to the fact that brands and trade names of drugs vary from country to country, making the completion of an international handbook an enormous challenge. After the review of several handbooks, the following 3 sources were used:

1. "Handbook of Drug Administration via Enteral Feeding Tubes" (3);
2. "Guia de Administração de Medicamentos por Sonda Nasogástrica" (19);
3. Summary of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) of medications.

The British handbook represented the most in-depth and up-to-date guide on administration of medications via EFT at the time of evaluation and it was used as our primary source of information. If the needed information could not be found there, the second source was consulted. The Portuguese guide has the advantage of addressing medications available in Portugal and was thus a useful tool to annex the primary source. In cases when inconsistencies arose between the two guides, the medication's SmPC and PIL were consulted. If the discrepancy could not be resolved, the information from the British handbook was accepted as most correct.

6.4 DATA COLLECTION FORM

The used form of data collection was derived from a form for collecting general medication errors[1], which was developed by a co-researcher as part of her previous work. It was remodeled based on the previous definition of MEs. It included general information on the patient, the drug therapy, the chart for evaluation of medication errors, the pharmacist interventions and suspected preventable ADEs (Attachments 3 and 4).

An additional data collection form was prepared for assessment of suspected preventable ADE. It summarized the basic information about the patient and the active substance, besides the strength, brand and dosage regimen of the medication investigated, the period of therapy, the period of intubation and the expected consequence of drug administration via EFT (dose-dumping and expected toxic serum levels, ineffectiveness due to crushing enteric coating). Furthermore, it included the Karch-Lasagna algorithm (13) for evaluation of severity of ADE and the Naranjo algorithm (12) for the assessment of the probability that a specific ME caused the suspected ADE (Attachment 5).

[1] Amaral J., et al. Registo e Classificação de Resultados Negativos associados à Medicação e de Intervenções Farmacêuticas em doentes internados e de ambulatório. Apresentação oral n.º 83. 13º Simpósio Nacional da A.P.F.H.: "Farmácia Hospitalar: o Doente – desafio de sempre". 18 Novembro de 2009 - Europarque, Santa Maria da Feira.

6.4.1 PILOT STUDY

In the first 3 weeks of June 2010, a pilot study including 10 patients was conducted on 3 wards. The data collection form was tested and minor modifications were done based on the results. Two new wards – Internal Medicine IA and IIA - were added to ensure a satisfactory number of patients with EFT.

After the pilot study, two slightly different versions of data collection forms were prepared for patients included in the intervention group and in the control group: the intervention group data collection form included a chart for suggested changes in drug therapy after review and additional comments.

6.5 DATA COLLECTION

The data collection was performed during a period of 2 months (1st July 2010 to 30th August 2010) and included 60 patients with EFT (30 per group).

Using the electronic system the researcher checked if newly hospitalized patients with EFT were reported or if any already hospitalized patient was newly reported with EFT. Since it was possible that not all intubated patients had the EFT reported in the electronic system, the researcher visited the wards and crosschecked the patient list. The check was done every morning of every weekday. Patients, who fulfilled the inclusion criteria, were randomly assigned to one of the groups.

Data from both groups were collected using the data collection forms. The researcher gathered data from patients in the intervention group every single day of the study, for maximum 10 consecutive days. Data from patients in the control group were gathered only once, 10 days after inclusion in the study. Data on prescribed and dispensed drugs as well as pharmacist interventions were collected from the electronic prescribing system and drug charts. Besides these data, the researcher also recorded if the use of EFT was reported in the electronic prescribing system.

As incorrect doses were counted doses of all administered medications, categorized as absolute prescribing errors and absolute dispensing errors.

The observation time was maximum 10 days and did not necessarily equal the hospitalization time of patients.

6.6 PREVENTABLE ADVERSE DRUG EVENTS ASSESSMENT

Patients with absolute prescribing and dispensing errors, excluding prescribing errors due to risk of exposure or contact sensitization, were selected only after collection and assessment of the data from all patients included in the study. The evaluator was a clinical pharmacist who was previously not involved in the study. He was given a short lecture on medication use in patients with EFT, its limitations and possible harms, and was familiarized with the report form. The researcher was available for possible questions and doubts throughout the assessment period.

Since the evaluator was not given any training on assessment of ADE, he was encouraged to consult Marimoto's article (11) on MEs and ADE for orientation and help.

For each case, the evaluator was given an assessment form. When administration of the investigated drug was expected to cause a dose-dump and toxic serum levels, notes on overdose symptoms obtained from Micromedex (20) were attached to the evaluation form. The evaluator was recommended to search data in the patient's clinical files, nurses' notes and laboratory exams, and was asked to assess a) the probability of a casual relationship between the ME and the ADE, and b) the severity of non-doubtful ADE.

6.7 STATISTICAL ANALYSIS

The data gathered were analyzed with the help of SPSS Statistics 17.0. General group characteristics and outcomes were compared according to frequencies where applicable; means were compared using the Student's t-test or chi-square test. In all cases, the assumed confidence interval was 95% and the P value less than 0.05 was considered statistically significant.

7 RESULTS

During the study period, 65 patients were included. However, 5 patients were excluded as they were intubated for less than 3 days. The two groups, the intervention group and the control group each consisted of 30 patients.

The results are presented in two sections: (1) section on the general characteristics of the groups, which presents and compares the basic information of patients from both groups, and (2) the outcome section, in which the main results of both groups are summarized and compared.

7.1 GENERAL CHARACTERISTICS

The general characteristics of both groups are summarized and compared in the table below.

Table V General characteristics of patients included in the control group and in the intervention group

	Control group	Intervention group	Statistical analysis
Age, median (range)	80,5 (33-93)	80,5 (36-94)	t-test, df=58, CI=95%, p=1
Gender, number of males (percentage)	17 (57)	13 (43)	Chi-square test, df=1, p=0,47
Ward, number of patients (percentage)			
- Med IA and Med IIA	20 (66)	19 (63)	Chi-square test, df=1, p=0,69
- ICU	6 (20)	5 (17)	
- Neurotrauma and Neurosurgery	4 (14)	6 (20)	
Number of oral medications prescribed, mean (total)	6,1 (183)	6,4 (190)	t-test, df=58, CI=95%, p=0,68
Number of days of observation, mean (range)	8,00 (3-10)	8,43 (3-10)	t-test, df=58, CI=95%, p=0,48

As can be observed from the statistical analysis column, group showed no significant difference in any of the general characteristics compared.

7.2 OUTCOMES

The main study outcomes - number of patients with non-reported EFT, number of medications lacking data on use via EFT, absolute prescribing and dispensing errors, relative prescribing and dispensing errors, number of suggested and accepted pharmacist interventions, number of incorrect doses administered and number of preventable ADEs - are summarised in Table 6.

7.2.1 NUMBER OF PATIENTS WITH NON-REPORTED EFT

In the electronic prescribing system, the administration of medicines through a feeding tube can be reported and is visible to the healthcare team in order to allow to suggest changes in therapy or adopt the correct means of administration. Data on the frequency of newly reported tubes was collected and resulted in 4 patients with non-reported EFT in the control group (n=30, 13%) and 11 patients in the working group (n=30, 37%). This made a proper assessment of the suitability of the drug therapy for EFT administration prior to drug dispensing impossible for the pharmacists in the control group. In the medications therapy of each of the 4 patients from the control group at least one non-corrected absolute prescribing error was observed. In the intervention group, the drug therapy was checked and interventions suggested no matter if the tube was reported or not.

7.2.2 NUMBER OF MEDICATIONS LACKING DATA ON USE VIA EFT

From consulting the selected literature it was obvious that information on the use of various medications through EFT was not available or insufficient. In the control group 25 such medications were encountered (n=183, 14%), while 38 medications were noted in the intervention group (n=190, 20%). The difference in the number of medications without information versus all medications investigated per patient between the two groups was not significant (t-test, p=0,218).

Table VI Primary and secondary outcomes

	Control group	Intervention group
Number of patients with non-reported EFT (percentage)	4/30 (13)	11/30 (37)
Number of drugs with no data on use via EFT (percentage)	25/183 (14)	38/190 (20)
Number of absolute prescribing errors (percentage)	20/183 (11)	15/190 (8)
Number of absolute dispensing errors (percentage)	15/183 (8)	7/190 (4)
- Errors not detected	13	1
- Errors detected, but interventions not accepted	0	6
- Errors impossible to detect*	2	0
Number of relative prescribing errors (percentage)	37/183 (20)	35/190 (18)
Number of relative dispensing errors (percentage)	35/183 (19)	20/190 (11)
Number of pharmacist interventions (percentage accepted)	16 (88)	90 (77)
- Interventions in absolute prescribing errors	5 (100)	14 (57)
- Interventions in relative prescribing errors	2 (50)	20 (66)
- Other	9 (78)	56 (85)
Number of incorrect doses administered	151	111
• Due to errors not detected	110	3
• Due to interventions not accepted	0	92
• Due to errors impossible to detect*	33	0
• Doses administered before the error was detected and corrected	8	16
Number of non-doubtful preventable ADE	**8**	**4**
• Due to errors not detected	6	1
• Due to interventions not accepted	0	3
• Due to errors impossible to detect*	1	0
• Due to doses administered before the error was detected and corrected	1	0

*EFT not reported in the electronic prescribing system

7.2.3 NUMBER OF ABSOLUTE PRESCRIBING AND DISPENSING MEDICATION ERRORS

The drugs that resulted in absolute prescribing errors are summarized in table 7. In the intervention group, these medications were prescribed 15 times compared to 20 prescriptions in the control group.

Table VII Drugs that results in absolute prescribing errors

DRUG	RECOMMENDATION FOR USE VIA EFT IN LITERATURE
Alfuzosin *PR tablets*	The patients should be advised to swallow the whole tablet. Other ways of administration like dividing, crushing or chewing should be avoided. Incorrect administraton can result in unwanted release and inadequate absorbtion of the active substance. [3]
Aminophylline *PR tablets*	Do not crush! Use injectable formulation as an alternative.[2] The tablets should be swallowed whole and should not be chewed.[3]
Chlorpromazin *Film-coated tablets*	Coated tablets. Do not crush. Risk of contact sensitisation. [1] Use oral solution as an alternative.[2]
Clarithromycin *Film-coated tablets*	No specific data available. Recommended use of oral suspension. Consider parental therapy or an alternative macrolide such as azithromycin.[1] Do not crush. Use alternative: clarithromycin oral suspension.[2] Tablets should be swallowed whole with a glass of water.[3]
Digoxin *Film-coated tablets*	Use liquid preparation.[1] It is not recommended to crush the medication due to its narrow therapeutic window. [2]
Nifedipine *PR tablets*	Prolonged-release preparation, do not crush. Change to immediate-release nifedipine or once-daily amlodipine.[1] Do not crush. As an alternative, administer immediate-release formulations through sub-lingual route.[2] The tablets should not be chewed or parted! [3]
Nitrofurantoin *Capsules*	Risk of contact sensitisation. Use liquid preparation.[1] It is not recommended to open the capsules.[2]
Potassium chloride *PR tablets*	Do not crush. Not suitable for administration via EFT.[1] The tablets should be swallowed whole with an adequate amount of

	liquid.[3]
Rifampicin *Capsules*	Risk of contact sensitisation. Use liquid preparation.[1]
Tamsulosin *PR capsules*	Formulation is unsuitable for administration via the feeding tube; consider changing to an alternative drug such as doxazosin.[1] Capsules should be swallowed whole with a glass of water. Never open or chew capsules in order not to interfere with the prolonged-release of the active substance. [3]
Valproic acid *Film-coated tablets* *GR tablets*	Tablets should be swallowed whole, without chewing. Never divide or crush tablets. [3]

[1] Handbook of drug administration via enteral feeding tubes.

[2] Guia de Administracao se Medicamentos por Sonda Nasogastrica

[3] SmPC or PIL

It has to be noted that prescription of esomeprazol gastro-resistant tablets (Nexium®) was not counted as a prescribing error. Although the formulation is a film-coated tablet containing enteric coated granules and thus should not be crushed, Nexium® is licensed for administration via EFT[2] and can therefore be prescribed to patients with EFT. However, the tablets are not allowed to be crushed, but should be dispersed in non-carbonated water in order not to interfere with the enteric coating of the granules. Esomeprazol gastro-resistant tablets were prescribed to 14 patients in the control group (47%) and 18 patients in the intervention group (60%).

Looking at the formulation type, prolonged-release formulations were the most common absolute prescribing errors and gastro-resistant formulations were the least frequent in both groups (Table 8).

[2] Nexium tablets (Astra Zeneca), Summary of Product Characteristics; September 2009.

Table VIII Absolute prescribing MEs per formulation type

	Control group	Intervention group
Number of absolute prescribing errors (percentage)	20/183 (11)	15/190 (8)
- Prolonged-release formulations	10/20 (50)	8/15 (53)
- Gastro-resistand formulations	1/20 (5)	3/15 (20)
- Other	9/20 (45)	4/15 (27)

The pharmacists intervened in 14 prescribing errors in the intervention group (n=15, 93%). However, 7 interventions were not accepted by the physicians. In one patient the researcher detected and attempted to correct the error as planned, but the patient was already discharged at the time of drug therapy checking, therefore the medication was not corrected during the observation time.

In the control group, pharmacists corrected 5 prescribing errors (25%), but failed to correct 13 errors (65%). In two patients with prescribing errors in their drug therapy, the use of EFT was not reported and therefore these medications could not be recognized as prescribing errors by the pharmacists.

The prescribing errors which were intervened by the pharmacists in the intervention group, but not accepted by physicians, involved the following formulation changes:

- Aminophylline prolonged-release tablets to aminophylline IV solution,
- Potassium chloride prolonged-release tablets to potassium chloride IV solution,
- Digoxin tablets to digoxin oral solution.

In the case of aminophylline and potassium chloride, the main reasons for rejecting the change of medication were cost-benefit hesitations. Change to IV formulation represented a major increase in costs. It was argued that the serum levels of both drugs were assessed daily through TDM and thus the potential toxic levels would be observed and the dosage corrected if needed. The physicians also complained of recurrent problems in achieving therapeutic serum levels of theophylline using aminophylline IV solution and were therefore reluctant to prescribe it.

In the case of digoxin an oral solution was not commercially available, but was prepared as an extemporaneous solution in the pharmacy of the main hospital of the CHLO hospital center. Change of the formulation represented additional costs and work. Thus it was decided not to change the formulation, but to monitor the digoxin serum levels through TDM and adjust the dose accordingly.

7.2.4 NUMBER OF RELATIVE PRESCRIBING AND DISPENSING ERRORS

MEDICATIONS WITH MORE ADEQUATE ALTERNATIVE IN THE SAME THERAPEUTIC GROUP

These type of errors were rare. According to the literature used, 5 medications (n=190, 3%) in the intervention group and 11 (n=183, 6%) in the control group might have been changed to a more appropriate alternative. The pharmacists in the intervention group agreed to intervene in only two cases, resulting in 3 relative dispensing errors. In the control group, one change was suggested and accepted, therefore 10 relative dispensing errors were detected. Most of the changes in both group comprised substitution of simvastatin film-coated tablets with atorvastation film-coated tablets due to better solubility.

MEDICATIONS WITH A LIQUID ALTERNATIVE FORMULATION

As relative prescribing and dispensing errors concerns it turned out that dispensing a solid formulation when a more appropriate alternative fomulation exists was a more frequent error than prescribing or dispensing medications that should never be used via EFT. All non-oral and oral liquid formulation were counted as a more appropriate alternative formulation. However, in practice all suggested alternatives were liquid formulations.

In the intervention group, 30 (16%) medications could have been exchanged with a liquid formulation. Two thirds were attempted to be intervened (n=20, 66%), but only 13 were actually changed due to lack of stock of medications. One third of possible changes were not suggested by the pharmacists due to professional doubts on the advantages of the change. Of all non-suggested changes, the majority involved change of paracetamol tablets to paracetamol paediatric oral solution.

From the 26 possible changes in the control group, only 1 (3,8%) was actually changed, in two patients the EFT was not reported and thus the relative prescribing error could not be detected. 23 possible changes were not suggested (89%), 10 of which similarly included the change of the paracetamol formulation.

Table IX Relative prescribing and dispensing errors

	Control group	Intervention group
Number of relative prescribing errors (percentage)	37/183 (20)	35/190 (18)
Number of relative dispensing errors (percentage)	35/183 (8)	20/190 (4)
- Change to alternative in the same therapeutic group	10	3
- Change to liquid formulation of the same drug	25	17

There was no significant difference in the number of medications with a more adequate alternative versus all investigated medications per patient between the two groups (t-test, p=0.79).

7.2.5 NUMBER OF PHARMACIST INTERVENTIONS SUGGESTED AND ACCEPTED

Besides detecting and correcting absolute and relative prescribing errors, pharmacists interventions consisted also of counselling on methods of correct administration of drugs via EFT, need to stop the feed due to possible interactions, monitoring on eventual adverse effects, etc.

In the intervention group, a total of 90 interventions were recorded, which was approximately 6 times more than in the control group (16). Most common interventions were providing information on correct use and administration of drugs or recommended a more appropriate alternative medication/formulation. In few cases, counseling on possible interactions, potential adverse reactions, or the need to monitor serum levels was observed. The percentage of interventions accepted by physicians and nurses in the intervention group was very high when providing information on medications and counselling on

interactions etc. (85%), but a significantly lower number of recommendations to change a medication were accepted (57% and 66%). In the control group, the overall acceptance precentage was high (88%). The difference between groups in the overall number of interventions for specific categories was significant (t-test, $p<0.01$).

Table X Types and frequency of suggested and accepted pharmacist interventions

	Control group	Intervention group
Number of pharmacist interventions (percentage accepted)	16 (88)	90 (77)
- Interventions in absolute prescribing errors	5 (100)	14 (57)
- Interventions in relative prescribing errors	2 (50)	20 (66)
- Correct administration, interactions, etc.	9 (78)	56 (85)

7.2.6 NUMBER OF INCORRECT DOSES ADMINISTERED

Failure to detect and correct prescribing errors resulted in dispensing incorrect medications for use via EFT. Since the nurses on the wards were not expected to change the medication formulation, it was assumed that all the dispensed medications have been administered as dispensed. Included were the doses of all dispensed medications with a prescribing error from both groups, even if the error was detected and corrected at any later point during the observation period.

In the control group, 155 incorrect doses were administered. The highest total number of incorrect administered doses resulted with aminophylline (28), the lowest with clarithromycin (4). The highest number of incorrect doses administered to one single patient was 27 doses of valproic acid gastro-resistant tablets. In the intervention group, 111 incorrect doses were administered. The vast majority (83%) were the consequence of prescribing and not accepting the change in the formulation of aminophylline prolonged-release tablets (42 doses in total) and potassium chloride prolonged-release tablets (45 doses in total).

For group comparison the number of incorrect doses administered per patient per observation day was calculated (Table 9). We have obtained this number by dividing the number of incorrect doses administered to each patient by the number of days of his observation and calculating the mean value in each group.

Table XI Maximum and mean number of incorrect doses administered per patient per observation day

	Control group	Intervention group
Maximum number of incorrect doses administered per patient per observation day		
• actual	3,0	3,0
• had all the interventions been accepted		0,6
Mean number of incorrect doses administered per patient per observation day		
• actual	0,6	0,4
• had the interventions been accepted		0,1

The highest mean number of incorrect doses administered was 0,6 per patient per observation day in the control group, which is as expected based on the number of absolute prescribing errors and dispensing errors. In the intervention group, each patient received on average 0,4 incorrect doses per observation day. However, if all the suggested pharmacist interventions had been accepted, this number would have been reduced for more than 4 times, resulting in 0,1 incorrect doses administered per patient per observation day.

Furthermore, comparing these results it can be noted that there is no significant difference between the number of incorrect doses administered per patient per day in the two groups (t-test, $p=0,13$). However, comparing the number of incorrect doses administered had the interventions been accepted the number of doses administered in the intervention group becomes significantly lower than in the control group (t-test, $p<0.01$).

7.2.7 SUSPECTED PREVENTABLE ADVERSE DRUG EVENTS

For the assessment of suspected preventable ADE all dispensed medications with absolute prescribing errors were included, except the medications that should not be crushed due to the possibility of exposure or contact sensitization. Preventable ADEs were suspected in 11 cases of the intervention group and 16 cases of the control group.

Table XII Probability and highest severity of suspected preventable ADE in the intervention group

DRUG	NUMBER OF INCORRECT DOSES	NUMBER OF NON-DOUBTFUL ADE VS. ALL SUSPECTED ADE	HIGHEST SEVERITY
Digoxin, Film-coated tablets 0,125 mg	5	0/1	NA
Valproic acid, GR tablets 500 mg Film-coated tablets 200 mg	8	0/3	NA
Aminophylline, PR tablets 225 mg	42	2/3	moderate
Tamsolusin, PR tablets 0.4 mg	2	1/1	mild
Potassium chloride, PR tablets 600 mg	45	1/2	moderate
Alfuzosin, PR tablets 10 mg	2	0/1	NA

Table XIII Probability and highest severity of suspected preventable ADE in the control group

DRUG	NUMBER OF INCORRECT DOSES	NUMBER OF NON-DOUBTFUL ADE VS. ALL SUSPECTED	HIGHEST SEVERITY
Digoxin, Film-coated tablets 0,125 mg, Film-coated tablets 0,25 mg	26	1/5	moderate
Valproic acid, GR tablets 500 mg	27	0/1	NA
Aminophylline, PR tablets 225 mg	28	2/2	moderate
Tamsolusin, PR tablets 0.4 mg	15	2/2	severe
Potassium chloride, PR tablets 600 mg	12	1/2	moderate
Nifedipine, LR tablets 20 mg, PR tablets 60 mg	16	2/4	severe

Tables 14 and 15 (next page) summarise the suspected and actual preventable ADE in both groups. The violet colour in table 15 denotes the patients with non-reported EFT, thus the prescribing errors could not be detected by pharmacists. The medications in green were changed to a more appropriate formulation by the pharmacists during the observation time.

The red colour represents medications that were intervened by pharmacists, but the interventions were not accepted; these constitute 92 of 111 incorrect doses administered (83%). In orange is shown the prescribing error that the researcher failed to correct during observation time. The rest of the incorrect doses were administered to patients in the first 24 hours after admission, which were allowed for usual clinical practice to occur and when no additional interventions were made on the behalf of pharmacists (see Materials and methods).

Table 16 explores the correlation between types of formulation and the probability of suspected preventable ADE.

Table XVI Probability ranking for suspected ADEs according to formulation type

	Number of suspected ADE	doubtful (percentage)	possible (percentage)	probable (percentage)	definite (percentage)
GR formulation	2	2 (100)	0 (0)	0 (0)	0 (0)
PR formulation	18	7 (39)	9 (50)	2 (11)	0 (0)
Other	7	6 (84)	0 (0)	1 (14)	0 (0)

Since all suspected ADE when administering gastro-resistant formulations were assessed as doubtful, the severity assessment in this formulation group was not applicable. However, for prolonged-release and other formulations Table 15 shows the correlation between the formulation and the severity of preventable ADE. The prolonged-release formulations - the most common prescribing error - had the highest probability (Table 16) and severity of suspected ADE (Table 17).

Table XIV Suspected and actual preventable ADE in the control group

DRUG	SUSPECTED ADE	OBSERVED ADE	PROBABILITY	SEVERITY
Digoxin Film-coated tablets 0,125 mg Film-coated tablets 0,25 mg	Hypo/hyperkalemia, nausea, vomiting, bradycardia	P1: no	doubtful	NA
		P2: hypokalemia and hyperkalemia	probable	moderate
		P3: no	doubtful	NA
		P4: no	doubtful	NA
		P5: no	doubtful	NA
Valproic acid GR tablets 500 mg	Drug ineffectiveness, worsening of symptoms	P1: no	doubtful	NA
Aminophylline PR tablets 225 mg	Tachycardia, hypotension, dysrhythmias, hypokalemia, hypophosphatemia, hypomagnesemia, hyperglycemia, leukocytosis	P1: tachycardia, hypotension, hyperglicemia,	possible	moderate
		P2: tachycardia, hypotension, hypokalemia	probable	moderate
Nifedipine PR tablets 20 mg PR tablets 60 mg	Bradycardia, hypotension, dizziness, fatigue, dysrhytmias, syncope, altered mental status, metabolic acidosis, hyperglicemia	P1: bradycardia, dysrhytmias, hyperglicemia	possible	severe
		P2: no	doubtful	NA
		P3: no	doubtful	NA
		P4: bradicardia, dysrhytmias	possible	moderate
Tamsolusin PR tablets 0.4 mg	Hypotension, tachycardia, dizziness, drowsiness, syncope	P1: hypotension	possible	moderate
		P2: Tachycardia, hypotension	possible	severe

Potassium chloride PR tablets 600 mg	Vomiting, diarrhea, weakness, muscle cramps, hypotension, dysrhytmias, hyperkalemia/hypokalemia	P1: no	doubtful	NA
		P2: hypokalemia	possible	moderate

Table XV Suspected and actual preventable ADE in the intervention group

DRUG	SUSPECTED ADE	OBSERVED ADE	PROBABILITY	SEVERITY
Digoxin Film-coated tablets 0,125 mg	Hypo/hyperkalemia, nausea, vomiting, bradycardia	P1: no	doubtful	NA
Valproic acid GR tablets 500 mg Film-coated tablets 200 mg	Drug ineffectiveness, worsening of symptoms	P1: no	doubtful	NA
		P2: no	doubtful	NA
		P3: no	doubtful	NA
Aminophylline PR tablets 225 mg	Tachycardia, hypotension, dysrhythmias, hypokalemia, hypophosphatemia, hypomagnesemia, hyperglycemia, leukocytosis	P1: tachycardia, hypokalemia	possible	moderate
		P2: tachycardia	probable	moderate
		P3: no	doubtful	NA
Tamsolusin PR tablets 0.4 mg	Hypotension, tachycardia, dizziness, drowsiness, syncope	P1: bradycardia	possible	mild
Potassium chloride PR tablets 600 mg	Vomiting, diarrhea, weakness, muscle cramps, hypotension, dysrhytmias, hyperkalemia/hypokalemia	P1: no	doubtful	NA
		P2: hypokalemia	possible	moderate
Alfuzosin PR tablets 10 mg	Hypotension, tachycardia, dizziness, drowsiness, syncope	P1: no	doubtful	NA

Table XVII Severity ranking of non-doubtful ADEs according to formulation type

	Number of ADE	mild (precentage)	moderate (precentage)	severe (precentage)	Lethal (precentage)
Prolonged-release	11	1 (9)	8 (73)	2 (18)	0 (0)
Other	1	0 (0)	1 (100)	0 (0)	0 (0)

The results for comparing the groups according to probability of preventable ADE are shown in Figure 6. In both groups, half or more suspected ADEs were assessed as doubtful. This mainly comprised gastro-resistant formulations, where the suspected ADE is attributable to drug ineffectiveness, and other drug formulations, which in our study was mainly digoxin.

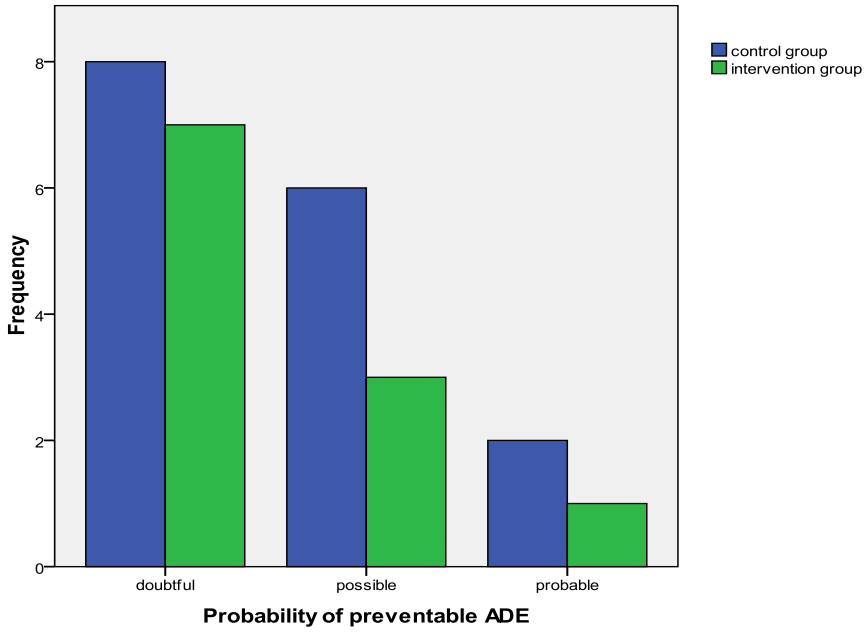

Figure 6 Probability of suspected ADE according to group

All non-doubtful ADEs were assessed according to severity (Figure 7). The probability ranking was comparable between the 2 groups, while ADEs in the control group were assessed as more severe than ADE in the intervention group. In the intervention group 3

out of 4 non-doubtful ADE were the consequence of non-accepted prescribing errors corrections (aminophylline PR tablets and potassium chloride PR tablets).

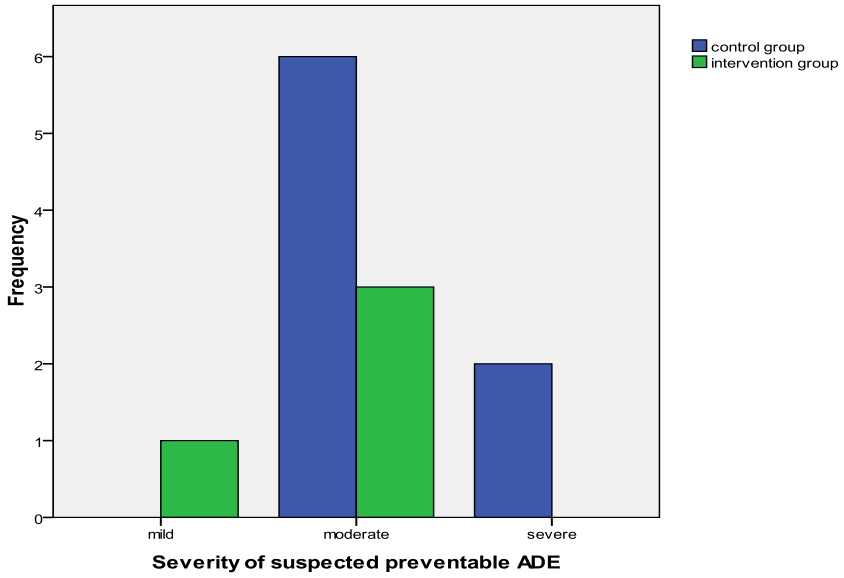

Figure 7 Severity of non-doubtful ADE according to group

Translating the frequency of ADE to a group of 100 patients, 27 non-doubtful preventable ADE occurred per 100 patients in the control group and 13 per 100 patients in the intervention group. Had all the pharmacist interventions been accepted, the rate in the intervention group would have fallen to 3 non-doubtful preventable ADE per 100 patients, which is 9 times less than in the control group.

According to severity, 20 moderate preventable ADE and 7 severe preventable ADE occurred per 100 patients in the control group. In the intervention group no severe preventable ADE was reported, however it had 3 mild and 10 moderate preventable ADE per 100 patients. All moderate preventable ADE in the intervention group were a consequence of not accepted prescribing corrections.

8 DISCUSSION

In the last decade, the use of enteral feeding has expanded due to its advantages over parenteral nutrition. The choice and administration of medications through EFT represents a challenge since it often requires careful formulation selection or it can result in ADEs. The presented prospective randomized control study attempted to investigate the effect of pharmacist interventions on the frequency of medication errors and adverse drug events in patients with EFT in a group, receiving additional pharmacist's services, and a group undergoing routine practice. To the best of our knowledge, this is the first randomised control study on medication errors in patients with EFT that attempted to assess the frequency of preventable ADEs in these patients.

8.1 STUDY LIMITATIONS

8.1.1 DEFINITIONS AND LITERATURE

An important limitation of the present study is the specific definition of the medication error, which made comparision with similar studies challenging. Furthermore, the detection and correction of medication errors were performed on the basis of a specific selection of literature dealing with medication administration via EFT. A different selection of literature might have given different results. However, differences arose mainly when comparing relative errors; absolute prescribing and dispensing errors did not differ considerably consulting various literature, thus the primary outcomes were not affected by this limitation.

8.1.2 STUDY DESIGN

The study design chosen was a quantitative, prospective randomized trial. Although RCT are the strongests study designs for quality control (21), they also have important drawbacks. One of the main bias which is likely to occur is the »contamination«, which is the impact of interventions intended for the intervention group on the control group: When pharmacists in the intervention group suggested changes in drug therapy, or shared data on correct administration, or changed the specific formulation, these interventions might have had a direct impact on the work of physicians, nurses and also other pharmacists.

Consequently, (a) the number of prescribing errors coul have been reduced as well as (b) of the percentage of suggested pharmacist intervention in the control group increased. The latter effect could have been proven by comparing the number of prescribing errors and pharmacist interventions in the control group in different periods of the study.

The contamination effect in both groups could have been avoided if a before-after study had been conducted along with the RCT. Applying the design of comparing outcomes before and after the study could show the rate of change above the background change and thus eliminate the degree of contamination in both groups. However, this design was not applied due to time and human resources limitations.

Although this bias was to a certain degree inevitable in the control group due to afternoon and weekend shifts, it was attempted to be reduced to the smallest degree possible by avoiding pharmacists included in the control group, to interact with patients in the intervention group. Moreover, the analysis of the distribution of prescribing errors throught time in the control group does not reveal a diminutive trend.

The sample size – 60 patients – was small.

8.1.3 DATA COLLECTION

As already pointed out, the pharmacist interventions were only followed through the electronic prescription system. Although all corrected prescribing errors and suggested formulation changes could be observed in the electronic system, personal or phone interventions, including consultations on correct administration of medications, interactions with feed, drug serum levels monitoring, were not detected. Therefore the observed frequency of pharmacist intervention in the control group is expected to have been higher than reported. It might be difficult to compare the frequency of pharmacists interventions with previous reported studies, since we only focused on interventions essential for medication use in patients with EFT. An important intervention, change of dose, was not included in the count.

8.1.4 PREVENTABLE ADVERSE DRUG EVENTS

Due to time and human resources limitations, assessment of preventable ADEs was performed only in patients with detected absolute prescribing and dispensing errors, in which a high probability of ADEs was expected. Potential ADEs resulting from prescribing medications, which should not be used via EFT due to risk of exposure or contact sensitisation of the healthcare team, were excluded. Such administration may however result in reduced effectiveness of the medication and therefore ADEs. All solid medications that were not categorised as prescribing errors, but that could be exchanged with a liquid formulation, were also not assessed for ADEs. ADEs as a consequence of drug interaction with feed were not studied.Consequently, the actual total number of preventable ADEs might have been higher than reported, although most likely on account of ADEs of low severity and low probability.

Furthermore, due to time limitations, the probability and severity of suspected ADE was assessed only by one evaluator. Assessment by two evaluators and use of the consensus method in cases of disagreement would increase the reliability of the gained results.

Assessment of the economic burden of the actual preventable ADEs would give the study an important added value.

8.2 GENERAL DISCUSSION

The principal findings of this study are a high rate of prescribing errors and preventable ADE in patients receiving medication therapy through EFT and the crucial role of pharmacists in preventing these errors.

8.2.1 PATIENT'S CHARACTERISTICS

The population studied comprised mostly elderly patients (median age 80.5 years) with an average of approximately 6 oral medications prescribed. More than half patients were hospitalised in the Internal medicine Ia and IIA wards, which were the largest of all wards included in the study, approximately one fifth of patients were included from the ICU. Only a few patients were hospitalised in the neurotrauma and neurosurgery wards, mainly because patients in neurotrauma were usually hospitalised for longer periods, thus not

many new patients were admitted and had the possibility to be included in the study. The drug therapy of patients was observed for 8 days in average. Study groups did not show significant difference in any general patients' characteristics.

8.2.2 REPORTING OF EFT USE THROUGH THE ELECTRONIC SYSTEM

From all patients, one quarter did not have their tube reported in the electronic prescribing system. This made the detection and correction of prescribing errors during pharmacist's prescription validation impossible. Furthermore, the system only allowed physicians to select »nasogastric tube« as the type of EFT used. If the patient was fed through a jejunostomy tube, this was not reported in the system or erraneously reported as feeding through nasogastric EFT. Both situations can lead to medication errors and ADEs. This observation supports the idea that although computerized physician order entry system may greatly reduce the frequency of medication errors, it can also facilitate certain types of errors (22).

8.2.3 DATA ON USE OF DRUGS VIA EFT

Although the literature selected offered in-depth information about the use of medications via EFT, this compiled database did not offer necessary data for 15 to 20 % of all medications investigated. As was observed through the assessment of suspected ADEs, the group of patients receiving medications via EFT is exposed to a high risk of harm, thus further investigations should be encouraged in order to obtain verified data on the use of medications via EFT. The pharmaceutical industry should be encouraged to conduct studies and include information on such use in the Summary Product Characteristics.

8.2.4 ABSOLUTE PRESCRIBING AND DISPENSING ERRORS

Prescribing errors occured in more than half the studied population, which reveals patients with EFT as notably susceptible to MEs. Most prescribing errors involved prolonged-release formulations, which are most alarming, due to dose-dumping and consequently possible drug-overdosage. The reasons behind such high frequency of prescribing errors were not analysed. However, comparing the number of prescribing errors in patients with reported or non-reported EFT showed no significant difference; these errors are thus unlikely to be the consequence of physician's unawareness of the

administration of medications via EFT. The reported rate of prescribing errors in the literature is very wide due to methodological study differences and differences in the study population (23). In our study, a prescribing error was redefined and a specific population was studied, which should be taken into account when comparing our results with previous studies. Nevertheless, it has been reported that the frequency of prescribing errors detected during pharmacists' review of medication orders is between 0.3 to 1.9% of all medications prescribed (24); in our study, the reported rate was 8 to 11% of all oral medications prescribed. This result is comparable with the reported rate of prescribing errors in paediatric inpatients (13.2%), who are regarded as one of the patient groups most exposed to MEs (25), evidencing that patients with EFT are similarly prone to MEs.

The reported dispensing error rate varies from 0% to 45%, although excluding the extremes, it is considered to be less than 1% (26). Our study revealed a much higher dispensing error rate (19% and 11%). Differences may again lie in the definition of dispensing error and the specific group type (see also The role of pharmacists).

8.2.5 RELATIVE PRESCRIBING AND DISPENSING ERRORS

The study results show that approximately 15% of all medications prescribed could have been replaced with a liquid formulation. If all prescribing errors arosen due to the prescription of a medicine that could be replaced with a therapetic alternative in a liquid formulation is added, the frequency increases to 20%. This result is comparable with a recent study on drug use in patients with EFT, which reported that 23% of prescribed solid oral medications could be replace by an alternative liquid formulation (18). Similarly as in the case of prescribing errors, the number of suggested changes of formulations was significantly higher in the intervention group.

It should also be taken into account that the patients were subjected to a rather high number of oral medications (6 to 7 per patient in average). In the comparable study previously mentioned (18), an average of 5 oral medications per patient was reported. The results presented here might be slightly higher due to the selected wards, age and clinical condition of the patients. The high number of oral medications enhances the necessity to change solid oral formulations to liquid to avoid EFT occlusion and possible interactions.

An unexpectably high number of changes were not suggested due to professional doubts. Most of the rejected changes included replacement of paracetamol film-coated tablets with paracetamol paediatric oral solution. Such change would require administration of large volumes of solution, which includes sorbitol as an excipient. The latter can in doses, higher than 15g per day, cause diarrhea and the advantage of the change was thus outweighed by the possible harm.

Besides changes to liquid formulations, more than half of the medications that could have been replaced by a more adequate alternative in the same therapeutic group were not changed. These changes are normally based on (a) an inadequate solubility of the drug (change of simvastatin to atorvastatin), (b) an attempt to reduce the dosage interval (propanolol to once daily atenolol) or (c) a change to a medication with a more appropriate formulation (e.g., lorazepam tablets to diazepam oral solution). The changes were perceived as unnecessary by both physicians and pharmacists in most cases. However, since ADEs were not investigated in these medications no conclusion can be made regarding the actual danger of their administration via EFT.

8.2.6 PREVENTABLE ADVERSE DRUG EVENTS

The incidence of non-doubtful preventable ADEs, 27 per 100 patients in the control group and 13 per 100 patients in the intervention group, was remarkably higher than the rate of general adverse events in the hospital setting reported by the European Commission (8% and 12%). (27) Yet again, such comparision might be far fetched. Disregarding the high frequency of doubtful ADEs and the fact that none was considered definite or lethal, specific trends can still be observed regarding the type od medications and ADEs.

The correlation of formulation type and probability and severity rates shows that administration of PR formulations brings patients to a high risk of moderate to severe ADE. Medications with the highest severity of ADE were nifedipine PR tablets and tamsulosin PR tablets, while aminophylline PR tablets resulted in moderate, but most probable ADE. Moreover, ADE after administering crushed GR formulations were all assessed as doubtful, since the consequence of an ineffective treatment may only develop after longer periods of inappropiate use. Nevertheless, ineffective treatment may have

notable consequences also in short-time treatment in certain groups of patients, e.g. in patients on ICU, who are expected to be under stress conditions.

Digoxin was found difficult to correlate with preventable ADE. It's inherent variability in bioavailability, distribution and excretion and the difference in effect depending on the clinical context, have probably influenced this result. Moreover, ECG tests, which could determine cardiac disturbances as a consequence of digoxin toxicity, were usually not performed (20). The high rate of doubtful and possible ADEs can also be associated with the hospitalization wards and the patients' critical clinical status. This demanded use of polypharmacy and frequent changes in medication therapy which resulted in the lack of an obvious correlation of a symptom with the specific medication investigated.

8.2.7 THE ROLE OF PHARMACISTS

Although the assessment of ADE was challenging and not all suspected preventable ADE resulted in actual ADE, pharmacist's role in preventing them is obvious. They revealed to be a key element in detecting and correcting prescribing MEs and thus preventing ADEs in this particular group of patients. The study shows that pharmacists can correct more than 90% of prescribing errors, significantly reduce the number of incorrect doses administered to patients and thus prevent the majority of tube-related ADEs. However, this can only be achieved through in-depth knowledge on the use of medication in patients with EFT and if provided enough time and resources for the provision of the service, offered to the intervention group. Therefore, this group of patient should be perceived as especially vulnerable that requires regular medication reviews. Pharmacists failed to detect and correct most of the prescribing errors through routine medication therapy check, even when use of EFT for medication administration was clearly stated in the computer prescription order. All errors corrected in the control group were attributed to the same pharmacist, who was in charge of the ICU ward and was performing ward visits on a regular basis (3 times per week). This supports the observation that pharmacists, present at ward-rounds, can have an outstanding role in detection and prevention of prescribing errors, this being true also for patients with EFT. (28) The reasons why pharmacists failed to detect prescribing errors were not examined. However, previous studies on pharmacists' detection of precribing errors, identified lack of alertness caused by enormous workload and fatigue as most common these reasons. (29). Taking into

account the specificity of the patient group, reasons might also include the pharmacists' failure in recognising the need for special attention in the patient's treatment or even lack of knowledge.

8.2.8 ACCEPTANCE OF PHARMACIST'S INTERVENTIONS

Physicians appeared reluctant in accepting changes suggested by pharmacists in the medication therapy of the studied patients. The overall acceptance rate in the intervention group was 77%, which is remarkably less than the acceptance rate of pharmacist interventions in the emergency department (89–98.6%) (30) or the acceptance rate of pharmacist interventions in prescribing in an acute-care hospital (88.8%) (31). The acceptance rate of interventions regarding change of formulation type was as low as 55%, even though many of these interventions attempted to correct absolute prescribing errors which had high probability to result in ADE. Reluctance to accept these interventions resulted in 4 non-doubtful ADEs, 3 of which were assessed as moderately severe. The acceptance rate in the control group (88%) was comparable with the general reported rate.

The physicians found the changes, especially in formulation, unnecessary in various cases. The main argument behind the rejected changes was monitoring of medications' serum levels through TDM. If crushing the prolonged-release medications has actually resulted in dose-dumping and toxic serum levels, that could be noted in the analysis results. However, comparision of the time of administration and the time of TDM revealed several discrepancies due to which the occurrence of dose-dumping and exposure to toxic serum levels could not be excluded nor detected by TDM if the latter was not adopted to the formulation change occuring during crushing of PR tablets. In one patient, aminophylline serum levels were, for example, measured more than 9 hours after administration, although peak serum levels occur 1-2 hours after administration. The TDM timing was probably selected due to the prolonged-release formulation and the peak serum levels were expected to occur later than in normal release, but in practice the formulation lost its prolonged-release properties due to crushing. The peak serum concentration was thus achieved earlier and could not be detected through TDM analysis. The same situation was repeated and occured in several other patients being administered aminophylline as well as digoxin and potassium chloride prolonged-release tablets. TDM can thus be an effective tool for

monitoring medication serum levels in patients with EFT, but should always be interpreted according to the medication type, the formulation and the overall condition of the patient.

8.2.9 RECOMMENDATIONS FOR IMPROVEMENT

Although the teaching hospital had an electronic prescribing system, through which the administration of drugs via EFT could be reported, all prescriptions were validated by pharmacists before dispensing and pharmacists were present regularly at the wards, the frequency of MEs and preventable ADEs in patients with EFT was still significant.

The study outcomes reveal several possibilities for improvement. The electronic prescribing system should be reorganised so that reporting of EFT should be mandatory for all intubated patients. Physicians as well as pharmacists should be specifically warned about the use of drugs via EFT through the system before prescribing and dispensing of drugs takes place. Warning on contraindication of drugs for use via EFT revealed to be effective in reducing administration errors in a recent study and this possibility should be investigated. (15)

Since MEs can arrise at any stage from prescribing to administration, the whole healthcare team should be aware of the vulnerability of patients with EFT and educated about the correct selection and administration of drugs in this group of patients. A protocol on correct drug use should be prepared and should be available to all helathcare team members. A drug database with information on all possible alternative formulations should be set up. Physicians and nurses should work closely with the pharmacists and should be encouraged to contact them in case of doubts on correct selection or administration of drugs via EFT.

9 Conclusions

We have conducted a prospective, randomised control trial comparing the frequency of medication errors and adverse drug events in patients with EFT in patients, receiving additional pharmacist's servises and patients undergoing routine practice. The study showed that:

- Patients with EFT revealed to be at a high risk of MEs and ADEs.
- The number of prescribing errors and dispensing errors was reduced in the intervention group.
- Pharmacists in the intervention group suggested more interventions than in the control group, but the acceptance rate was low.
- Acceptance of all pharmacist interventions can significantly reduce the number of incorrect doses administered.
- Acceptance of all pharmacist interventions can reduce the number of ADEs.

Patients with EFT should always receive extensive drug therapy review as was performed in the intervention group.

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11 ATTACHMENTS

ATTACHMENT 1: NARANJO ALGORITHM

Question	Yes	No	Do Not Know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	

Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30:239-245.

Scoring

> 9 = definite ADR

5-8 = probable ADR

1-4 = possible ADR

0 = doubtful ADR

ATTACHMENT 2: KARCH-LASAGNA SCALE

Severity	Description
Mild	No antidote or treatment is required; hospitalization is not prolonged
Moderate	A change in treatment (e.g., modified dosage, addition of a drug), but not necessarily discontinuation of the drug, is required; hospitalization may be prolonged, or specific treatment may be required
Severe	An ADR is potentially life threatening and requires discontinuation of the drug and specific treatment of the ADR
Lethal	An ADR directly or indirectly contributes to a patient's death

ATTACHMENT 3: DATA COLLECTION FORM CONTROL GROUP

ATTACHMENT 4: DATA COLLECTION FORM INTERVENTION GROUP

ATTACHMENT 5: ADE EVALUATION FORM

Examiner:

_____

PATIENT INFORMATION

Sex:	**Age**:	**Weight**:	**Ward**:	**Code**:
Diagnose:				

DRUG SUSPECTED

Active substance, brand	**Strength**	**Dosage regimen**	**Treatment start/end - reason**	**Intubation start / end**

Period of intubation and treatment:	
Expected consequence of administration:	
Time of administration	**Serum levels (teofilina)**
Expected symptoms	**Symptoms present?**
Use of specific drugs suggesting ADE	**Specific drugs used?**
Laboratory triggers	**Laboratory results present?**

SEVERITY EVALUATION: KARCH-LASAGNA SCALE

Severity	Description
Mild	No antidote or treatment is required; hospitalization is not prolonged
Moderate	A change in treatment (e.g., modified dosage, addition of a drug), but not necessarily discontinuation of the drug, is required; hospitalization may be prolonged, or specific treatment may be required
Severe	An ADR is potentially life threatening and requires discontinuation of the drug and specific treatment of the ADR
Lethal	An ADR directly or indirectly contributes to a patient's death

Lethal **Severe** **Moderate** **Mild**

PROBABILITY EVALUATION: NARANJO ALOGIRTM

Question	Yes	No	Do Not Know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued	+1	0	0	

or a specific antagonist was administered?				
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	

Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30:239-245.

Scoring

> 9 = definite ADR

5-8 = probable ADR

1-4 = possible ADR

0 = doubtful ADR

Date: _____

Examiner signature: