

THERAPEUTIC ERROR : TYPES AND PREVENTION STRATEGIES AND FOCUS ABOUT "LOOK ALIKE/SOUND ALIKE" AND "HIGH RISK" DRUGS

ABSTRACT

Introduction: Therapeutic errors are among the main causes of drug-related problems, in terms of enhanced toxicological or reduced therapeutic effect, and concern all stages of the drug chain, from manufacturing to prescription, dispensing and administration. Everyone, pharmacists and doctors in all settings, should be aware of how to prevent and manage them and which drugs are at greatest risk. In this article we will focus on LASA (look alike/sound alike), on FAR (high-risk drugs) and on the guidelines especially for prevention.

methods: the article is a minireview that was written by research in paper and online on PubMed and Embase. We performed a search of any publications available in these databases between the years 1990 and 2022, using the key words: therapeutic errors, misuse / diversion of drugs, drug poisoning. After a review of the titles and abstracts, the articles chosen were considered relevant in providing evidence of the problem. We also added personal knowledge about the topic of the article and used some paper documents.

Discussion and conclusions: Most of the errors in therapy occur during administration, due to errors in doses, posology or interactions or incorrect manipulations of pharmaceutical forms, and in dispensing, due to incorrect interpretation of the prescription or confusion on the packaging in the case of LASAs. Pharmacists and doctors but also patients themselves should pay attention to the time of prescription and doctors to the drug history not only for interactions but also to avoid making mistakes in patients who take drugs with names or packages similar to the one described above. Moreover, attention must be paid in writing the prescription, in dosage, and pharmaceutical forms. Particular attention should be paid to handling by children and to avoiding any misuse of the medicines themselves.

keywords: pharmacovigilance, medication errors, drug misuse, clinical toxicology

INTRODUCTION

According to the definition proposed by the National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP), “*therapeutic error*” means any adverse, undesirable, unintentional, and preventable event which may cause or lead to inappropriate use of the drug or a danger to the patient¹. Such an episode can be due to an error in the prescription, transmission of the prescription, labeling, packaging or denomination, preparation, dispensing, distribution, administration, education, monitoring, and use². Whether pharmacovigilance evaluates adverse drug reactions linked to the pharmacological properties and therefore intrinsic to the drug itself, the evaluation of the therapy error is mainly based on the methods of use of the drug and the risk clinical that can result from it (From July 2012, with the entry into force of the new European legislation as defined by EU regulation 1235/2010 and by directive 2010/84 / EU, it is expected that also all adverse drug reactions (ADRs) that occur due to medication errors (ME), abuse, misuse, the interaction between drugs, off-label use, and occupational exposure are reported). In particular, therapeutic errors occur at every stage of the process, especially in the administration phase (more than 53% of all errors). Other errors occur in the moment of prescription (16.5%), transcription (11%), and preparation (13.5%) of the pharmaceutical form. By “clinical risk” we mean the statistical probability that a patient is a victim of a severe adverse event, that is, suffers any “damage or discomfort attributable, even if involuntarily, to treatment medical services provided during the hospitalization period, which causes an extension of the period of hospitalization, a worsening of the condition of health or death ”. ³ The phenomenon of drug poisoning is also reported by poison centers (CAV) in Italy: 34% of requests for consultancy are linked to drug-related accidents; these data are in line with what was observed at an international level. The US Joint Commission on Accreditation of Healthcare Organization (JCAHO) has identified *sentinel events* (i.e. events serious, often avoidable related to the treatment and assistance provided),

collected through a process of spontaneous reporting, as some indicators for patient safety including therapy error.⁴ Sentinel events determined by errors of therapy are considered so relevant to the safety of patients who have been placed within one of the five areas considered priorities for the development of quality indicators by the Organization for Economic Co-operation and Development (OECD). Mistakes of therapy that lead to death or serious complications are located within the "events area sentinel".⁵The interventions aimed at preventing therapy errors mainly concern two areas: that of the drug and the more complex one of therapy management.⁶The Risk Management System consists of a set of activities aimed at identifying, characterizing, preventing, or minimizing the risks related to medicinal products. In this article, we want to describe the main clinical risk prevention activities, in particular, relating to LASA (look alike sound alike, i.e. those drugs that compared to others already on the market have similar trade names or packaging and can therefore be easily confused with each other) and the FAR (drugs with high clinical risk, i.e. those drugs that require particular attention in the management e use, due to their potential toxicity, the low therapeutic index and the high possibility of interactions).^{7,8}

METHODS

The article was written by research in paper and online on PubMed and Embase. We performed a search of any publications available in these databases between the years 1990 and 2022, using the keywords: misuse / diversion of drugs, drug poisoning. After a review of the titles and abstracts, the articles chosen were considered relevant in providing evidence of the problem. We also added personal knowledge about the topic of the article and used some paper documents.

RESULTS AND DISCUSSION

Various types of therapeutic errors have been described:

- *Drug exchange error* is an accidental event related above all to medicines that have packs or similar names. The exchange can also concern drugs that provide different dosages for age groups but have identical packaging (for example Tachipirina suppositories 125, 250, 500, and

1000 mg). The presence of the pictogram affixed to self-medication drugs can facilitate the error (eg: Alginor for adults and children). It should be emphasized that the administration to a pediatric patient on an adult formulation drug almost always leads to an overdose.^{9,10}

- *Dosing errors* may occur due to pro/dose or pro/day misunderstandings. The error for a single dose can occur because milliliters are confused with milligrams, or the number of drops with milliliters, milligrams, or even with the number of measuring cups/droppers / bottles (e.g. 3 droppers instead of 3 drops). For example, we recall the case of a patient who was prescribed methadone 120 milligrams a day who, taking it with a syringe instead of the appropriate measuring cup, turned out to be taking 12 a day and not 120 with therapeutic insufficiency.^{11,12}

- The *error by way of administration* consists byof taking the drug with routes other than those indicated for the formulation of the product (parenteral use or inhalation of preparations per os / external use; ocular/nasal administration of oral preparations / external/parenteral use or ingestion of preparations for external use/inhalation / parenteral use). This can lead to serious undesirable effects such as gastrointestinal irritation due to exposure to acidic/basic substances, excessive or insufficient absorption of the active ingredient, and toxic or pharmacological actions related to specific excipients.^{13,14}

- *miscellaneous*: The *error of preparation* occurs with the use of drugs that require suspension/mixing of the solute with the solvent, that can be taken without the solute or the solute without the solvent or they can be added to the suspension of the inert parts of the package (desiccant granules, wrappers).¹⁵This type of error can be very serious for some types of drugs (for example concentrated electrolytic solutions containing, for example, potassium, administered without dilution). Among the drugs most frequently involved in pediatric age, powdered antibiotics to be suspended are reported. The *error due to expiration* concerns the consumption of drugs beyond the expiration date or after several days from impromptu preparation. This is the only error that generally doesn't involve acute toxicological problems, even if it is possible that, in the case of preparations in suspension or drops, the active ingredient is more concentrated by evaporation of the solvent.^{16,17} The *pharmacist's mistake*, who provides a drug other than that indicated on the

prescription, can be for incorrect reading of the recipe or for accidental exchange with such a place in the same drawer.¹⁸

In the context of therapy errors there are some types of drugs particularly exposed not only to the frequency of development from errors but above all to severe reactions consequent to them:

- LASA drugs (look alike-sound alike), for which the ministry of health already issued a recommendation for the prevention of errors in 2010 aimed at all healthcare professionals
- FAR (high-risk drugs), of which the SIFO (hospital pharmacy company) has not only drawn up a detailed list but also guidelines for the prevention of the related clinical risk.^{19,20}

drugs with high clinical risk (according to 2015 SIFO guidelines)

- Adrenergic agonists and antagonists for venous use,
- General Anesthetics, Antiarrhythmics, and IV Antithrombotics,
- Cardioplegic solutions, parenteral and oral chemotherapy drugs
- Glucose, hypertonic solutions ($\geq 20\%$) Solutions for dialysis, Drugs administered epidurally and intrathecally, Oral hypoglycemic agents
- IV inotropic agents,
- Insulin under the skin and ev
- Liposomal drugs (eg liposomal amphotericin B)
- iv benzodiazepines, opioids, iv, transdermal and oral (including concentrated solutions and immediate or modified release formulations), neuromuscular blockers, iv contrast media
- Solutions for total parenteral nutrition, IV hypertonic sodium chloride in concentration $> 0.9\%$.^{21,22,23}

SPECIFIC DRUGS:

Adrenaline under the skin, IV Epoprostenol, IV and subcutaneous insulin, Magnesium sulfate for injection, oral Methotrexate for non-oncological use, Opium tincture, Oxytocin iv, Sodium nitroprusside for injection, Concentrated potassium chloride for injection, Potassium phosphate for injection, Promethazine IV, IV or intraosseous vasopressin

Therapeutic errors are more frequent in particular among the elderly and children for at least two reasons²¹:

- Both of these categories are more frequently exposed to the need for handling pharmaceutical forms, especially for swallowing problems. Manipulation is often done by the patient or caregiver in an inadequate manner and this, especially in the case of drugs with a low therapeutic index, can more easily produce acute problems of overdose or side effects^{22,23}. Manipulation is often done by the patient or caregiver in an inadequate manner and this, especially in the case of drugs with a low therapeutic index, can more easily produce acute problems of overdose or side effects. In the case of children, due to the lower body weight, even relatively modest doses can more easily generate serious pictures of toxicity, especially because many drugs used in pediatrics only used off-label, starting from formulations for adults and extrapolating the dose in an indirect way.

- The elderly patient is often in a condition of polytherapy. "Polypharmacy" means the intake of more than 5 drugs a day, a phenomenon that affects over 20% of the general population and 50% of the geriatric population; we start with "excess" if the drugs are over 10 per day, which happens in over 10% of the elderly). It is in fact known that it is precisely the pro-die pharmacological load that is proportional to the risk of developing ADR²⁴; for this reason, lists of potentially inappropriate drugs in the elderly have been drawn up which the doctor can use, of which the best known are the list of criteria proposed by Beers and those Stopp and Start. Adverse events are numerous in pediatric and geriatric wards, given the type of treated patients, in oncology wards and in diabetic patients or patients suffering from pathologies cardiovascular in therapy with insulin and anticoagulants, given the toxicity of the drugs used. Pediatric patients are more exposed than adults to potentially dangerous medication errors²⁵. Since the pharmacokinetic parameters vary according to age, there is a need to calculate individual doses based on the patient's age, weight (mg / kg), body surface area (mg / m²) and clinical conditions.

polypharmacotherapy and risk of therapeutic error in the elderly

The intake of several drugs per day, a typical condition of the elderly, can derive both from the physical comorbidity in the individual patient and from the need to treat single pathologies with combinations of several drugs (as occurs for diseases such as hypertension, diabetes, tumors, COPD etc ... typical pathologies of the geriatric age). To these are added medicines often taken for intercurrent problems such as antibiotics or analgesics sometimes, especially in the latter case, for self-medication (OTC or SOP in Italy). Polytherapy can increase the risk of therapeutic errors especially in some cases: patients assisted by several caregivers, elderly patients who live alone, patients with cognitive deficit^{26,27}. Exchange of drug packs, supra-therapeutic intake of single drugs due to forgotten previous intake, dose errors (both pro / dose and pro / day) or excessively long intake times are some examples of typical problems. To these can be added errors in the handling of solid forms in particular (especially in dysphagia patients) and interactions with food or other co-taken drugs. Two important goals of geriatric assessment are:

- frequently reassess the patient and the real need to take certain drugs, providing, where possible, periods of scaling or suspension of certain therapies such as, for example, cardiovascular or respiratory drugs in the summer
- consider, according to the Beers and START / STOPP criteria, drugs potentially inappropriate or worthy of particular monitoring in the elderly, but also pay attention to the individual pharmaceutical forms and the initial pharmacological history, avoiding, if possible, prescribing medicines with similar names or packs to these patients

There are several recommendations referring to different operators involved in the “drug chain”; limiting itself to the useful elements about the patient to avoid therapeutic errors, some guidelines recommend^{28,29,30}:

1. Regarding the prescription, try to make it as clear as possible by avoiding abbreviations or terms that are ambiguous or difficult to interpret, in particular with regard to dosage and posology
2. remind patients to keep drugs out of reach of children, especially those at higher risk, by placing them in places that are difficult to access³¹
3. in the case of patients in polypharmacy, especially with medicines with similar names, possibly advise the patient to keep a “diary”, which can also be a simple paper or notebook, where the type of medicine is reported time and doses administered, thus avoiding errors such as forgetting to administer one compound or overdose of another
4. Be very careful when prescribing medicines in liquid form, especially if they have a low therapeutic index and require administration by syringe or measuring cup as the risk of administering non-therapeutic doses is particularly high, especially at the beginning of therapy³².
5. Also advise patients to have medicines with similar names in different places in their homes, so as to make the exchange of packs less likely
6. in the case of foreign patients, possibly attach together with the prescription and possibly the therapeutic plan, a sheet translated into their mother language on how to take the drug in order to avoid any linguistic misunderstandings
7. remind patients that modified release solid pharmaceutical forms or gastro-resistant film coated forms cannot be divided or crushed, unless the package leaflet is explicitly stated, and that some liquid forms such as oral drops may require dilution in water prior to administration. Also remember that drugs should not be mixed together but taken separately
8. when giving liquid medications to a child, keep in mind that the measuring cups and droppers are often calibrated for adult doses, and therefore may require adjustments in use^{33,34}

role of packaging in therapeutic errors

The pharmaceutical preparations are dispensed in a separate container in primary, ie the one in contact directly with the product, and secondary, i.e. the outer packaging. Based on the type of packaging we can distinguish the pharmaceutical forms in mono or multidose. In the case of liquid pharmaceutical forms, especially multidose, there may be errors in taking the right dose, in particular through the use of droppers, measuring cups, spoons or syringes. moreover, the closure should be guaranteed to prevent accidental opening of the primary packaging by children and for this there are specific adapted containers on the market. The same applies to the blister pockets, for which, especially for some medicines, they are packaged "break-proof", with a special seal that limits the ease of opening, especially for children.

CONCLUSIONS

Errors during therapy are the most frequent cause of clinical problems related to the use of drugs, especially in children and the elderly; it is, therefore, important for all healthcare professionals directly involved in the handling of the drug (doctors, nurses, and pharmacists) to know which are the most frequent, the drugs most at risk of developing them and above all, to know the main guidelines both for the prevention of clinical risk and for any treatment. The two moments with a major risk of making mistakes are the prescription and administration; in the first case, it is the task of the prescriber to ensure that the patient receives the right therapy, not only in terms of the molecule but also in pharmaceutical form, route of administration and without any interactions with other drugs or foods, trying to promote adherence and explaining the correct way of taking the drug. In the case of administration, on the other hand, it's the duty of the nurse or caregiver or the patient himself to ensure that the previous instructions provided by the doctor are correctly followed. Finally, it's the pharmacist's task to supervise the entire process, from prescribing appropriateness to methods of administration, and dispensing of the drug to interactions, safety, and adherence and, if necessary, make himself available to the patient or caregiver to provide explanations on any unclear aspects of the prescription.^{33,34}

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