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Wrong administration route of medications in the domestic setting: a review of an underestimated public health topic

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Abstract

Introduction

Since medication errors related to incorrect administration routes are less common than other errors, they are rarely considered when assessing patient mistakes. The present review was performed to search for papers assessing incorrect route medication errors made by adult patients with the aim of providing an overview of this phenomenon.

Areas covered

PubMed, Scopus and EMBASE were searched up to October 2019 using free text and MeSH terms, returning 7609 results. Papers were considered eligible if they considered incorrect administration route errors by adult patients in domestic settings. Finally, 11 papers were included, primarily from National Poison Centers (NPCs) or similar institutions from USA or Europe (observation period: 1985-2014). The data showed how an incorrect route of self-administration is a concern for patient safety and should be considered when evaluating medication errors. Moreover, one of the main observations that the results highlighted was the difficulty of obtaining clear and precise data regarding self-administration.

Expert opinion

NPC reports are a reliable but not exhaustive tool due to high underreporting; reports should provide additional information or insights into these issues. Additionally, improvements in drug packaging and labeling, proper plain language instruction and patient education could reduce the frequency of such errors.

Keywords: Accidents, Home; Health communication; Medication errors; Self-administration error; Incorrect administration route

Article highlights:

- Incorrect administration route errors constitute an under recognized portion of all medication errors
- There is difficulty in obtaining clear and precise data about self-administration errors, mainly due to high underreporting
- Poison centers represent a source of valuable surveillance data
- Reports should provide additional information on incorrect route administration errors to clarify the settings where errors are made
- Improvements in drug labels, packages and instructions could reduce the risk of involuntary administration errors

1. Introduction

A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient [1], and it has been defined as “the failure to complete a planned action as intended or the use of a wrong plan to achieve an aim” [2].

Although medication errors in the hospital setting are widely reported in the international literature and represent a serious threat to patients' health [3,4], other settings and timings have also been studied in relation to medication errors. For instance, the discontinuity of care from the inpatient to outpatient setting has been reported as a high-risk setting for medication discrepancies, which can possibly lead to an increased risk of rehospitalization [5,6]. In fact, mistakes are also made by the patients themselves or by their caregivers [7]. Indeed, the percentage of adult patients who make at least one medication error is approximately 12-59% [7]. Moreover, this percentage is 75% among older people who suffer from two or more diseases and consume more than five different drugs daily [7].

Medication errors related to the incorrect route of administration are rarely considered in scientific works that analyze mistakes made by patients. However, case reports of adult patients who self-administered medications through the wrong route have been widely reported. For instance, in 1984, Huntley reported two accidental ingestions of topical drugs [8]. The first case concerned a 56-year-old woman with widespread psoriasis: she ingested two potassium permanganate tablets (325 mg each) with 300 mL of water instead of using these medications for dissolution in bathwater. In the second case, a 36-year-old man with tuberous sclerosis ingested one packet of Burow's solution (aluminum triacetate) dissolved in a glass of water instead of using it topically on a wound infection. Fortunately, there were no severe consequences, but the author underlined the need for a change in packaging to prevent these types of errors [8]. In 1988, another case involved a 46-year-old man with hypertension who ingested nitroglycerine patches, thus showing that some patients require additional clarification to ensure the proper use of patches [9].

These cases may seem to be from the distant past, but in Italy, several accidents were recorded between 2005 and 2010. In particular, Settimi et al. found 215 cases of incorrect routes of administration of benzydamine-HCl in terms of oral consumption of a gynecological topical preparation. Many of these cases occurred after an advertisement that seemed to confuse people, highlighting the need to pay attention to drug advertisements and to monitor medication errors before, during and after advertising [10].

In addition to advertisements, many reports and papers have highlighted the role played by graphics on medication packaging and labeling in determining medication errors [11–15]. A review published in 2015 highlighted the lack of scientific evidence useful to improve the age appropriateness of the design of medicines for older adults, despite several claims [16].

Mistakes among elderly people may occur from difficulty reading the small print on labels due to visual acuity deficiencies or improper use of corrective lenses [17]. Measures from supervisory bodies are limited: the European Commission considered a font size of 9 points (measured in Times New Roman) as a minimum in its guideline on the readability of drug labeling and packaging [18], while the FDA [19] stated a minimum of a 10-point size font for Medication Guides: both sizes are not easily readable by the many people with vision impairments [17] and none of the organizations provides a different disposition or dimension for the instructions regarding the route of administration. This topic is particularly current, given the high consumption of over-the-counter (OTC) drugs [20-22], where no contact with a physician is required, and for proper drug consumption, it is necessary to rely on exhaustive leaflets, labeling and clear instructions on the package.

To our knowledge, no previous review has assessed the topic of incorrect routes of administration therapeutic errors in an outpatient or domestic setting perspective. There is no secondary literature about therapeutic errors focusing on the drugs most prone to this kind of error among the general public or among vulnerable population groups. In light of the above, we decided to perform a review of the literature searching for papers assessing incorrect

administration route medication errors made by adult patients to provide an overview of this phenomenon, to explore their frequencies and characteristics, and to understand the relevance of this topic for public health and health communication.

2. Body

2.1 Methods

Multiple search strategies were used to screen the existing data with the aim of estimating cases of self-administered incorrect route medication errors. The search was carried out in October 2019 on MEDLINE via the PubMed interface and Scopus databases. At a later stage, the search was extended in EMBASE, considering all records up to October 2019. Due to the purely observational nature of the research question, we used a search strategy not guided by a specific technique (e.g., PICO).

The MEDLINE search string combined exploded MeSH (Medical Subject Headings) terms such as *Drug Administration Routes*, *Accidents* and *Medication Errors* with a free text search. Scopus and EMBASE searches were conducted with the same strategy, adapting the string to the different syntax used in each database. The complete string is available in the Supplementary Material.

Three researchers (DC, GLM and GV) evaluated the records for eligibility, considering the inclusion criteria. A first selection was performed considering the Title and Abstract to define papers eligible for full-text reading. A second selection was performed on the full text. Papers in both steps of the selection process were assessed by two of the authors working independently and blindly; disagreements were resolved by discussion with the third researcher. The focus of the present study was to specifically evaluate medication errors made by adult patients who unintentionally self-administered an actual medication using the incorrect administration route.

The papers were considered eligible for inclusion if:

- They were written in English

- They considered incorrect route administration errors of drugs
- They considered such errors if made by adult patients
- They considered such errors if made in domestic settings
- They were full papers presenting original data published with peer-reviewed processes in scientific journals.

Additionally, papers were excluded if:

- They considered recreational, illicit, or veterinary drugs
- They focused on underdosing/overdosing errors and incorrect administration techniques through the right route of administration
- They focused on errors made by adults in their role as caregivers
- They provide a single or a small number of cases (case reports or case series publication types)
- They were qualitative studies

The researchers, solving any discrepancies by consensus, independently extracted data from the selected studies, collecting information about the country, observation period, the observed population, the age of the population, nonintentionality, setting, information source, main results and additional evidence.

2.2 Results

The total of the considered studies was 7609. As reported in Figure 1, selection based on title and abstract resulted in 95 studies selected for full-text analysis. Then, the authors decide to widen the search via *citation chasing* by looking for eligible articles in the selected papers' bibliography and articles quoting them. The whole selection phase resulted in 11 publications included for the review. Figure 1 represents an overview of the entire search process depicted as a PRISMA flow diagram, including the update procedure.

The results are summarized in *Table 1*: eleven articles were included in the final assessment. Among these, there was the above-described Italian report about benzydamine-HCl ingestions

[10]. The included papers were published between 1993 [23] and 2017 [24], with an observation period that ranged from 1985 [25] to 2014 [26]. Most of the papers included presented data from the United States of America [23-25,27-29] or Europe [10,26,30,31], while one paper reported data from Israel [32]. Although focusing on different subpopulations, the majority of the selected studies used data from national poison centers or similar institutions [10,23-26,28-32].

Regrettably, very important features such as age, domestic setting, nonintentionality, and self-administration were not clearly reported in each article, and specific data about such features were not provided for each kind of error. Specifically, the self-administration of the medication was a characteristic rarely reported: 9 papers out of 11 did not specify the percentage of errors made by the patients themselves. However, we decided to keep all of the papers that gave information about incorrect route administration errors that could potentially contain unintentional errors made by adult individuals in domestic settings to provide an overview of the frequency of this event. For these reasons, Table 1 shows the sample characteristics of each selected paper, allowing us to contextualize in more detail the incorrect administration route errors reported.

The first study, published by *Kroner* and colleagues [23] in 1993, was performed at the Virginia Poison Center (VPC) in the USA, considering all calls for people aged 60 years and older during a period of six months from October 1991 to March 1992. The authors reviewed 231 cases of exposure in the elderly. The majority of the exposures occurred in the home (84%), and only 10% took place in healthcare facilities; however, it was not possible to differentiate self-administrations. Accidental exposures were 84%, and the most frequent route of exposure was ingestion (71.3%). Unintentional incorrect route administration errors occurred in 28 cases (12.1%): 20 cases concerned the ingestion of an external product, while other products were inappropriately used as eye drops (6 cases) or as a topical preparation (2 cases) [23].

In 1994, *Rose et al.* collected all minoxidil exposures reported to the American Association of Poison Control Centers' (AAPCC) National Data Collection System from 1985 to 1991 (inclusive) [25]. Such exposures were 285, which is 0.003% of all exposures reported to the AAPCC in the same period. A total of 40.7% of cases occurred in people aged above 17 years. The majority of exposures were not intentional (83.9%) or acute (95.8%), and ingestion was the most frequent administration route (78.6%). There were 110 incorrect administration route errors (38.6%): in 76 cases, a 2% topical solution was ingested, and in 34 cases, there was ocular exposure. Among the cases of fatal, major or moderate outcomes (18 cases), one adult unintentionally ingested a topical solution (5.6%) [25].

The investigation performed by *Phillips et al.* in 2001 [27] is based on Individual Safety Reports (ISR), pieces of information stored in the Adverse Event Reporting System (AERS) database, which included all adverse events that had death as an outcome, coded as “drug maladministration” that occurred between January 1993 and December 1998. The included reports were from the USA and foreign countries from manufacturers that had a drug application filed with the US Food and Drug Administration (FDA). Not all of the errors occurred in an out-of-hospital setting. Specifically, regarding the setting, the hospital was the setting of 46.7% of the “Drug Maladministration” reports, followed by 14.9% in patients’ homes, 4.7% in ambulatory pharmacies, 4.7% in physicians’ offices, 4.5% at other sites and 24.5% not stated in the report. An incorrect route of administration was the third most prevalent type of error, with 57 records (9.5%) among a total of 5366 reports identified. The specific errors were intrathecal instead of intravenous (14 cases), intravenous instead of oral (8 cases), and intravenous instead of intramuscular or vice versa (5 cases), consisting of 4.6% of all errors and 47.4% of the incorrect route of administration errors, while the “other” category (30 cases) represented 5.1% of all errors and 52.6% of the incorrect route of administration errors. This paper highlighted the severity of incorrect route administration errors, leading to one-tenth of drug maladministration errors that had death as an outcome. Regrettably, this report did not classify the events by setting,

which reduces the information about the actual number of therapeutic errors made by patients during self-administration in a domestic setting. However, although incorrect routes of administration errors involving parenteral administration were specified, it is worth noting that over half of these errors were classified as “other” and could potentially be made by patients in domestic settings [27].

A report from *Ballesteros et al.* [31] in 2009 studied the in-depth ingestion of benzydamine-containing vaginal preparations through calls addressed to the Spanish Poison Control Center (SPCC) from 1991 to 2003. As mentioned above [10], people who use these gynecological formulations might make administration route errors by ingesting these medications. Indeed, 724 cases were recognized: 94.3% occurred in a home setting, and 52.9% occurred in a general public setting with no healthcare professional involved as an intermediary figure. Specifically, 86.2% of the patients were older than 14 years of age; among these, 80.9% were female. These errors are probably associated with the confounding effect of finding the same active substance in OTC solutions for oropharyngeal diseases. In particular, the authors reported that female adults (80.9% of adults) confused the route of administration of the drug, whereas male patients confused the medication with the oral antiseptic with the same active substance but different doses. The clinical effect of benzydamine poisoning was mild: 72.9% of cases were considered asymptomatic with minor symptoms, 25.7% with a moderate presentation, and 1.4% with severe symptomatology, none of which resulted in death [31].

The abovementioned publication by *Settimi et al.* considers the same medication errors considered by *Ballesteros* and colleagues. In Italy, from 2005 to 2010, the authors found 215 cases of oral consumption of gynecological forms of benzydamine-HCl, which were sold concentrated or as a powder to be dissolved in water [10]. This research focused on the association between the cases and three time periods (*preadvertisement*, during the *advertisement* and *postadvertisement*). In the *preadvertisement* period, the most common cause of incorrect administration route in women was confusion between two medications in 52.2% of

67 cases. During the broadcast time of the *advertisement*, the error was due to an incorrect route of administration in 81.2% of 64 cases, diminishing to 55.4% in the *postadvertisement* period. The reported increase in cases related to the incorrect administration route is acknowledged by the authors to be related to a misleading advertisement, and the confusing effect on the population did not cease after clarifying the topical-only use of this preparation in a subsequent commercial spot [10].

Hayes and colleagues [29] focused only on unintentional therapeutic errors among adults aged 65 recorded in data from the National Poison Data System (NPDS) of the USA, a database that includes calls to Poison Control Centers. A total of 140,786 older adults reported therapeutic errors, mainly originating from residence or other nonhealthcare facility locations. Major effects occurred in 486 cases (1.0%), and death occurred in 110 (0.2%). The incorrect administration route was the 6th scenario out of 16, with a total of 9,356 cases (6.6%). Specifically, the incorrect dosing route errors led to 3 deaths, 10 cases with major effects, 1,219 with moderate effects, 179 with minor effects, and 1,419 with no effect. However, 2,218 cases were not further followed because they were considered nontoxic, 4,197 were not followed because minimal effects were expected, and 111 cases were considered potentially toxic, but follow-up was not possible. It is essential to state that Hayes and colleagues did not specify which percentage of incorrect administration route errors was self-administered. However, the authors clarified that 45% of the cases of “health professional or iatrogenic errors” were concurrent with other scenarios. In particular, the most frequently other specified scenarios were the incorrect medication given, inadvertently given someone else’s medication, an incorrect dosing route, other incorrect dose, incorrect formulation or concentration dispensed, and 10-fold dosing error [29].

Shah and colleagues [28] published data from the National Poison Data System (NPDS) of the USA, carrying out an analysis only focused on unintentional therapeutic errors occurring in a location different from a healthcare facility (e.g., home, school, and workplace). From 2000 to

2005, the NPDS reported 1,166,116 cases with this feature. The majority of records were coded as no effect or not followed due to no effect expected (true nontoxic exposures), and 229 (0.01%) deaths occurred. The most frequent scenario was ‘took or gave medication twice’ (34%), while the incorrect administration route represented 2.9% (34,152 cases) of all out-of-hospital medication errors. It is worth noting that 6,010 children aged less than 6 years were included in the data of the incorrect dosing route [28].

In addition, *Cassidy* et al. examined the medication errors reported to the National Poisons Information Center (NPIC) of Ireland from 2007 to 2009 [30]. For this report, a medication error was defined as “any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer” and categorized as a prescribing, dispensing or administration error. Accidents that occurred in all clinical and domestic settings were included. The paper showed that the majority of medication errors (90.9%) reported occurred in a domestic setting and that the wrong administration route represented 9.1% (103 cases) of all of the types of medication errors reported to NPICs in the adult population (1,128 cases). In particular, 59 notifications referred to tiotropium bromide monohydrate, an inhalation powder contained in a gel capsule. A total of 58 patients ingested the capsule instead of inhaling the powder. The authors stated that the data shown in the report were poorly representative of the real proportion of medication errors and that, in addition, nonsevere medication errors in the domestic setting could be underestimated. In fact, the notifications were made using a phone number addressed to healthcare professionals, and the service was not advertised to members of the general public [30].

Another report, published in 2014 by *Lavon* et al. [32] from the Israel National Poison Information Center, provides information on medication errors occurring outside healthcare facilities. In this case, medication error was defined as an unintentional therapeutic error, considering unintentional any case of erroneous intake of a drug due to any error at any stage of the medication process. Among the 1,381 cases evaluated, adults accounted for just 28.7% of the

cases, and OTC medication was responsible for nearly half of the notifications (47.9%). The incorrect route of administration represented 2.1% (29 cases) of all types of medication error (1354). Moreover, the responsibility for the mistake was a parent in 56% of cases, the patient in 31.5%, a caregiver in 6.7% and a healthcare professional in 2.9% [32].

In 2015, *Urban and colleagues* [26] presented data from phone calls to the Toxicology Information Center (TIC) in Prague, serving the entire Czech Republic population. The authors performed a retrospective analysis of unintentional medication errors between 2013 and 2014, resulting in 1,354 calls by laypersons. Children were again the subjects of most of the calls, and only 38% of the reports referred to adults (age ≥ 20). The overall prognosis was favorable or rather favorable in 91.8% of cases. A mistaken route of administration was reported in 2.2% of all of the cases; the most common error was oral instead of topical application (application onto the skin, conjunctiva, ear, or nose), followed by vaginal and rectal administration or inhalation; less frequently, there were vice versa applications. The drug under consideration was the patient's own medication for the majority of the subjects (57.7%) [26].

Last, *Hodges and colleagues* [24] examined data from the NPDS of the USA to investigate unintentional medication errors in nonhealth care facilities (i.e., a residence, workplace, school, restaurant/food service, public area, other, or unknown) that resulted in the most clinically significant ("moderate effect," "major effect," "death," or "death, indirect report") medical outcomes, selecting 67,603 cases from 2000 to 2012. The majority of the reported medical outcomes had a moderate effect (93.5%). Most exposures occurred at their own residence, and the most frequent errors were "other incorrect dose", followed by incorrect medication taken/given and inadvertently took/given a medication twice. The incorrect dosing route was the 10th scenario out of 16, representing 2.3% (1,581 cases) of all nonhealth care facility serious errors. Specifically, 109 cases occurred in children aged 5 years or less, 80 in children aged 6-12 years, 95 in adolescents aged 13-19 years, and 1290 in adults aged 20 years or more, while in 7 cases, the subject's age was unknown [24].

3. Conclusion

In the present review, we focused on incorrect route administration errors made by adult patients in domestic settings, making it clear that such mistakes exist and that strategies to improve the understanding of the right administration route and communication with patients must be planned. Moreover, one of the main observations that the results highlighted was the difficulty of obtaining clear and precise data about self-administration.

Nevertheless, as our findings showed, the National Poison Centers databases can represent a valuable source of surveillance data, representing an important tool for reporting [23,25,28-30]. It must be stated that the actual incidence of medication errors occurring in a domestic setting is possibly much higher, considering that only a small number of cases are reported to poison centers due to asymptomatic patients or undetected errors [33].

Indeed, the use of data from this kind of large database can present several limitations. For instance, there might be improper coding, even if standard definitions exist, and a significant amount of unknown information due to the use of the “other” categories [24,28]. Moreover, the lack of health literacy may hinder patients from even recognizing an error [28], and the voluntary nature of the reporting to poison centers leads to reporting bias [28,29].

In addition, while therapeutic errors are considered unintentional by definition [34], not every source of information provided cases in this fashion exclusively; for example, Kroner [23], Rose [25], and Ballesteros [31] also included intentional exposures.

The present work had some strengths and limitations that should be acknowledged. A first limitation was associated with the generally poor quality of data that can be found in the scientific literature. In fact, no specific high-quality studies have been conducted to evaluate the frequency of self-administered medication errors due to incorrect administration routes in the domestic setting or to prevent these errors. Second, language restrictions in our search strategy have led to a narrow range of papers included in the evaluation, as periodical reports from poison

centers are occasionally published in non-English journals and/or nonindexed journals and are not included in this review. Nevertheless, the aim of this paper was to provide an overview of an under recognized issue. To our knowledge, the present work was the first to attempt to provide an estimate of the frequency of such issues, paving the way for specific studies. In fact, further studies need to be performed to investigate the reason for incorrect administration route errors and strategies to prevent them to increase patient safety.

4. Expert opinion

Medication errors represent a significant public health issue that must be faced to reduce patient harm, and incorrect administration route errors constitute a notable proportion of medication errors. In the Annual Report of the American Association of Poison Control Centers' NPDS outlines, more than 10,000 exposure cases reported to U.S. Poison Centers in 2018 were due to incorrect dosing routes, and more than 71% of them were in subjects older than 20 years old [35]. Despite the staggering number of cases, this represents a decrease in the frequency compared with previous reports. In fact, since 2006, the number of cases reported to the U.S. Poison centers due to incorrect dosing routes consistently exceeded 10,000, reaching peaks in 2010, 2011 and 2012, when more than 16,000 exposure cases were reported to U.S. Poison Centers [36-47]. It must be clarified that the data from the Annual Report of the American Association of Poison Control Centers' National Poison Data System considers all of the cases reported to the U.S. Poison centers, regardless of age, site of application or if they were intentional or unintentional.

Understanding the circumstances that lead to incorrect administration route accidents is crucial to develop preventive strategies to enhance patient safety [26,48-53].

To increase the knowledge about this kind of error and to design better strategies against such errors, we strongly believe that poison centers should develop a system of revision of reports. These centers could provide periodical cause-specific insights and in-depth analyses of the

characteristics of the errors, e.g., the most common drugs and routes, settings and administration dynamics.

Although the percentage of people incurring this type of error appears narrow compared with other therapeutic accidents, from the patient's perspective, no event is of little interest if potentially harmful. This is especially true when the patient is both the victim and the perpetrator, as frequently happens with this kind of therapeutic error.

It has to be stated that all patients would probably benefit from proper education [24] and from improvements in packaging, labeling and dosing instructions, but this is especially true for those with limited health literacy and numeracy [7,54]. Special and prominent instructions, such as images or infographics, should be given if the administration route differs from oral intake. In fact, the present review clearly established that the most frequent error consisted of oral consumption instead of a wide range of topical routes, [10,26,30,31] underlining that more needs to be done to develop intelligible packaging and clearer instruction leaflets [11–15].

In addition, information material specially designed for particularly vulnerable risk groups such as visually impaired people and low literacy-skilled patients should be limited in length, as well as in complexity [54], and have a larger font size [17] or color differentiation [7] to decrease the probability of errors in such categories [29]. In this regard, interestingly, the California Senate independently passed a legislation mandating lettering of a minimum of 12 points in size and requiring a patient-centered placement of information and increased regulation on this topic [17]. A study published in 2013 showed that participants given “plain language” instructions had a significantly better understanding of how to self-administer medication, and patients' ability to comprehend health-related information was improved using easy-to-read health information [55].

Last, the results showed the importance of healthcare professionals giving clear instructions and ensuring that the instructions are understood by patients or caregivers. The high percentage of medication errors associated with over-the-counter drugs has been associated with the lack of

proper instruction in a domestic setting [32,56]. Therefore, healthcare professionals such as pharmacists, physicians and nurses can play a key role, especially if the medication and dosing choice is unknown [28], and engaging in effective communication is crucial to avoid medication errors associated with incorrect routes of administration.

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