International Journal of Risk & Safety in Medicine 31 (2020) 133–144
DOI 10.3233/JRS-200002
IOS Press

Review Article

Patient safety issues associated with the use of compounded medicines as alternatives to approved pharmaceutical products in Europe and how best practice can improve outcomes

Mike Isles*
The European Alliance for Access to Safe Medicines, 20 Madeira Park, Tunbridge Wells, Kent, UK

Received 13 January 2020
Accepted 28 April 2020

Abstract.
BACKGROUND: Pharmaceutical compounding allows individuals with special requirements access to medicines. Compounding can also be used to provide cheaper alternatives to commercially produced medicines which may be less strictly regulated than those commercially produced as they do not require marketing authorisation.
OBJECTIVE: This review describes the issues and potential risks associated with compounded medicines and equally importantly identifies best practices.
METHODS: To establish reports about lack of effectiveness, adverse events and medication errors occurring with compounded pharmaceuticals, a literature search was conducted of PubMed, Embase and MEDLINE databases for relevant cases in European countries which were published between 2003 and 2018. Case reports/series that described instances of successful use of compounded medicines over the same period were also identified.
RESULTS: Overall, 12 case reports/case series describing problems associated with compounded medicines in Europe have been identified. Sources of patient risk associated with compounded medicines include lack of quality, safety and efficacy data, preparation and labelling errors, and improper storage and handling practices.
CONCLUSIONS: Several case reports/series describing instances of overdose, medication errors and adverse events associated with compounded medications were reviewed. The number of affected patients was relatively small, but many were children and two adult patients experienced permanent sequelae. The number of incidents associated with compounded medicines is unknown, and so these numbers should be interpreted with caution. When licensed medicines are available, the use of compounded medicines can put patients at unnecessary risk which should be avoided. Stricter regulation is necessary to prevent similar cases from occurring in the future as the European market for compounded medications grows. Pharmacists can promote best practices in compounding through professional organisations. Future recommended actions are: 1. Stricter regulation is necessary to prevent similar cases from occurring in the future as the European market for compounded medications grows. 2. A comprehensive pan-European survey to gain a greater understanding of compounding procedures and techniques. This would provide valuable information to the benefit of hospital systems and their patients. 3. The results of the survey can then be used to improve the knowledge and quality control of compounded medicines for the good of patient safety.

Keywords: Compounding, medication errors, patient risk, best practice, stricter regulation, complaints procedures, storage stability

*Address for correspondence: The European Alliance for Access to Safe Medicines, 20 Madeira Park, Tunbridge Wells, Kent TN2 5S, UK. Tel.: +44 (0)7540 462 867; E-mail: mike.isles@eaasm.eu.

1. Introduction

Pharmacy compounding is defined as "the combining, mixing or altering of ingredients to produce a customised medication" [1]. Until the 1950s, approximately 80% of all prescriptions were filled using compounded medicines [2]. However, today over 90% of medicinal products are industrially produced [2]. Despite this, the practice of pharmaceutical compounding remains necessary because it allows individuals with special requirements to have access to medicines [1]. Even when a licensed medicine is available for a particular condition, pharmaceutical compounding may be used to provide a cheaper alternative, but the process of compounding or reformulating the licensed medicine may introduce safety risks associated with the non-licensed formulation.

In many jurisdictions, compounded medicines are less strictly regulated than industrially produced medicines [1,3,4]. In Europe, compounded medicines are regulated at the national level and, in some cases, exempt from the rules that govern the industrial production [GMP]), distribution [GDP]) and use of medicinal products [2,5,6]. In the USA, compounded medicines are largely exempt from the Food and Drug Administration's (FDA) oversight. Regulation occurs at the state level through local boards of pharmacy [1,3]. As a result of this variable regulatory environment, compounded medicines have caused harm to patients, ranging from temporary discomfort to permanent debilitating adverse events (AEs) and death [1,3,7].

The aim of this review is to describe the issues and potential risks associated with compounded medicines, as well as best practice approaches that can help to avoid them.

2. Regulatory issues related to compounding

By law, regulatory authorities such as the European Medicines Agency (EMA) in the European Economic Area or the FDA in the USA must issue a marketing authorisation before a commercially produced medicine can be made available to the public [1,8]. Marketing authorisation is granted if the EMA is satisfied that quality, safety and efficacy criteria are met [9]. The FDA grants marketing approval when provided with "evidence consisting of adequate and well-controlled investigations by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labelling" [7]. Pharmaceutical companies are also obliged to report AEs associated with the use of their products [1,9].

In contrast, no such evidence is required for compounded medicines (Table 1). Both in Europe and the USA, compounded medicines are separated into those prepared in accordance with a prescription for an individual patient and those prepared in larger quantities and kept at hospitals for later use [10,11]. In Europe, these are referred to as 'magistral formulae' and 'officinal formulae', respectively. For the latter group, a product dossier is required to justify the formulation and preparation method used, while no such dossiers are required for the former group as it may delay the supply of the necessary medication [10]. In the USA, pharmacies that compound medicines in accordance with an individual prescription are referred to as 'traditional compounders', while those that compound medicines in bulk are called 'outsourcing facilities' [11]. Only outsourcing facilities are required to report AEs [11]. For the most part, information about the safety and effectiveness of compounded medicines comes from spontaneous reports of individual cases [1,7]. Spontaneous reporting has been shown to underestimate the incidence

Table 1
Differences between compounded medicines and industrially produced drugs [1]

	Industrially produced medicines	Compounded medicines
Marketing authorisation	• Evidence demonstrating safety and effectiveness in treating a particular condition must be provided	• Not required
Preparation	• Must comply with GMP	• In many jurisdictions, GMP compliance not required
Labelling	• Standardised • Contents regulated	• Not standardised • Contents not regulated
Pharmacovigilance	• Reporting of adverse events required	• Reporting of adverse events not required

GMP; Good Manufacturing Practice.

and severity of adverse reactions associated with a medicine [12]. It is also believed to introduce biases which distort the known safety profile of a medicine [12]. As a result, spontaneous reports of individual cases are likely to not be representative of the real-world performance of compounded medicines [1,7,12]. This is one of the reasons why the safety and effectiveness of compounded drugs cannot be guaranteed [1].

GMP guidelines have been designed to prevent errors during the production process [2]. In the EU and USA, all pharmaceutical companies must follow GMP [1,2] and their facilities are regularly inspected to confirm compliance [1,3]. In contrast, requirements for compounding pharmacies are less stringent and more variable, and compliance may not be closely monitored. In Europe, application of GMP to compounded medicines is recommended for 'high-risk preparations' only [10,13]. In the USA, outsourcing facilities are required to follow GMP, while traditional compounders are not. Traditional compounders also rarely undergo inspections [1,3,11]. As a result, compounded medicines have much higher content variability and fail analytical testing much more frequently than industrially produced drugs [3,14].

3. Methods

In order to identify case reports about lack of effectiveness, adverse events and medication errors that occurred with the use of compounded pharmaceuticals, a literature search was conducted of PubMed, Embase and MEDLINE databases (Table S1) on 21 and 27 June 2018 for relevant cases in European countries and were published between 2003 and 2018. Case reports/series that described instances of successful use of compounded medicines over the same period were also identified. These results were supplemented by ad hoc searches to identify relevant publications.

4. Results

Overall, 12 case reports/case series describing problems associated with compounded medicines in Europe have been identified which included 26 patients (Table S2). Six of the reports were from Belgium, two from France and one report each from Germany, Italy, Slovenia and Spain (Fig. 1). Five case reports/case series that described successful use of compounded medicines were identified (Table S3)

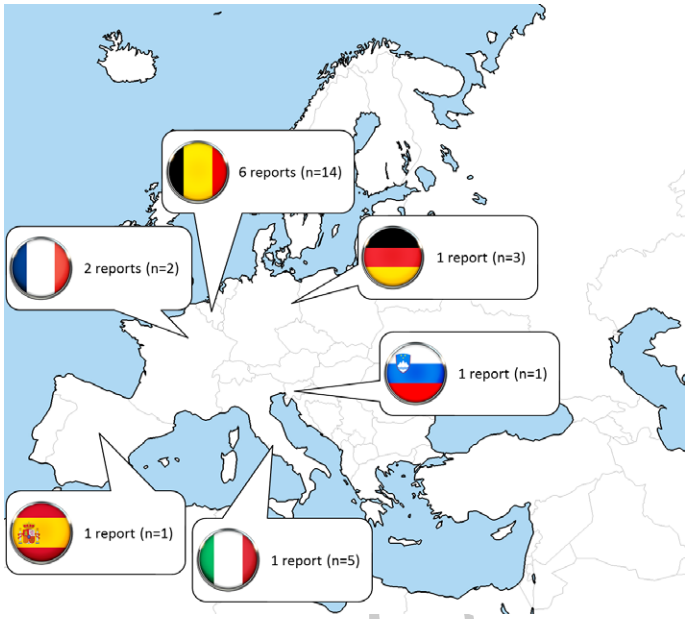

Fig. 1. Map of the case reports and case series describing instances of lack of effectiveness, adverse events and medication errors associated with the use of compounded medications that occurred in European Union-member states between 2003 and 2018.

[15–19]. These reports included a total of 93 patients, most (n = 77) from a single case series that, in addition to patients from Europe, included patients from Brazil [19]. Other publications described 16 patients. Represented European countries included France, The Netherlands and Spain.

Sources of patient risk associated with compounded medicines include lack of quality, safety and efficacy data, preparation and labelling errors, and improper storage and handling practices. These risks are described below using case reports/series identified during the search, as well as other relevant publications. Description of risks is followed by a section on best practice recommendations derived from publications of successful use of compounded medicines that were also identified during the search.

4.1. Issues around marketing authorisation

Carefully controlled clinical studies are necessary to adequately assess the safety and efficacy of a new medicine. However, some compounded medicines have never undergone such rigorous testing and as such bypass the existing regulatory hurdles, which results in a medicine being dispensed to a patient without the full profile of the chemical entity being known.

This can give rise to patient safety issues which are illustrated by the unlicensed medicine 4-aminopyridine (4-AP). For many years, 4-AP has been prescribed in the absence of regulatory approval/-marketing authorisation [7]. When systematic research was conducted, 4-AP was found to cause disorientation, seizures and encephalopathy in patients who received doses above 10 mg/day, underlining the need for comprehensive testing (that would have included establishing the therapeutic window). Such testing is required by medical authorities such as the EMA or FDA [7,20].

A case report of a patient with giardiasis was successfully treated with mepacrine in France demonstrates how compounded substances that have not received marketing authorisation can be used successfully [15]. The patient had giardiasis that was resistant to a range of approved drugs, including

metronidazole, albendazole and paromomycin. A search for alternative treatments showed that mepacrine could be used; however, it was not approved for use in Europe. A single manufacturer of the active pharmaceutical ingredient (API) was identified in India. No authorisation is required in France for importing an API if it is intended to be used in compounding. To ensure that the API was of the desired quality for clinical use, a range of quality control analyses were performed, including thin-layer chromatography, nuclear magnetic resonance and infrared spectroscopy. The results conformed to the values listed in the British Pharmacopoeia (BP) and in the relevant literature. The imported mepacrine was compounded with microcrystalline cellulose into capsules and the patient received 100 mg three times a day over the course of 10 days. Giardia parasites disappeared from stools after seven days of treatment and were absent after three months. No serious adverse events occurred [15]. This case illustrates that, for substances without marketing authorisation in the country where they will be prescribed to the patient, pharmacies need to analyse the imported API to ensure that it meets the standards as laid down in such established references as the BP before using it in a compounded formulation.

4.2. Preparation or manufacture

Errors in the preparation of a compounded medicine were the definitive or most likely cause of seven reports involving 17 patients [21–28].

Three 3-year-old boys (triplets) were admitted to an emergency department in Germany after they were found asleep and unresponsive [24]. Three hours prior, all three had received 1–2 drops of compounded nasal drops. The drops were later found to contain 20.0 mg/mL of xylometazoline (2%), i.e. 40 times the expected dose of 0.05%. The label for the compounded drops reported a dose of 0.5 g of xylometazoline per 10 mL (5%), which is 100 times the approved dose for children. All three children received intravenous fluid management; for two, no other interventions were required. One child with low oxygen saturation (85–88%) received supplemental oxygen via a face mask (3 L/min). This patient also had a respiratory rate of 15–20 breaths/min, sinus bradycardia (64 beats/min) and supraventricular extrasystoles. Two of the boys were awake 11 hours after the administration of nasal drops, while the third awoke 20 hours after the administration. Toxicological analyses of the patients' urine revealed xylometazoline concentrations of between 1.7 and 6.6 mg/L. All three were discharged the next day without neurological sequelae.

In Belgium, a pharmacist used a self-prepared nasal decongestant solution containing naphazoline 1 mg/mL and phenylephrine 2.5 mg/mL as a diluent to reconstitute seven antibiotic suspensions intended for paediatric patients [26]. As soon as he discovered the mistake, the pharmacist contacted the parents. Of the seven children who received the erroneous preparation, six presented to an emergency department of a local hospital. Patients were aged between 16 months and 12 years and had received between 2 and 12 doses of the solution (4–5 mL). The most common symptoms were bradycardia ($n = 6$), pallor ($n = 6$) and somnolence ($n = 5$); other symptoms were vomiting ($n = 3$), diaphoresis ($n = 2$), headache ($n = 2$), photophobia ($n = 2$) and ataxia ($n = 1$). The two children with headache and photophobia were an 8-year-old boy, who ingested 55 mg of naphazoline and 137.5 mg of phenylephrine over a 3–4-day period, and his older sister, for whom only limited information was available. The boy was kept under observation for five days, while the symptoms in the other six children resolved within 24 hours. All patients recovered.

A 58-year-old woman with secondary progressive multiple sclerosis (MS) was admitted to an emergency department in Belgium in a coma and with convulsive status epilepticus [23]. She had previously been treated with 4-aminopyridine (4-AP) 10 mg twice daily for over three years. Her symptoms were severe abdominal pain after taking one pill from a box of pharmacy-compounded 4-AP. Within one hour ocular revulsion, altered consciousness and tonic-clonic seizures developed. The patient was intubated

and treated with three different anti-epileptic drugs. During the initial 36 hours, electroencephalogram (EEG) showed abundant interictal epileptiform waves, predominantly in the left hemisphere. Epileptiform waves disappeared on subsequent EEGs, which remained slow and asymmetrical. The patient regained consciousness slowly and remained seriously encephalopathic. After three months, the patient had more pronounced spastic paraparesis and cognitive impairment, which improved slowly. An inquiry at the pharmacy showed that the compounded pill contained 100 mg of 4-AP instead of 10 mg.

In addition, three reports of overdose (three patients, including a newborn) [22,25,27], two reports of drug substitution (four patients) [21,28] and two reports where the error was not specified (two patients) [29,30], have been identified (Table S2).

4.3. Labelling

Medications produced industrially under GMP are required to have standardised labels and the content of these labels is strictly regulated [1]. There are no such requirements for compounded medicines [1]. Erroneous labelling was the primary reason for one of the cases described here [31].

A 40-year-old woman was admitted to the Percy Military Hospital in France for Hodgkin's lymphoma and was prescribed medication that included intravenous vincristine 1.4 mg/m^2 once weekly [31]. The hospital used the Asclepios2® software to create prescriptions. This software calculates body surface area and dose, and produces a label for the medication. Both the physician and the pharmacist were required to validate a prescription before it could be filled. However, the software programmer had incorrectly entered subcutaneous route of administration for vincristine, an error which was not detected by the prescribing physician or the hospital pharmacist who checked the label prior to administration. During the first administration cycle, an experienced nurse ignored the label and administered vincristine by intravenous injection. However, during the second cycle, a less experienced nurse administered vincristine in accordance with the erroneous label. A cutaneous erythema 5 cm in diameter developed at the injection site. The patient recovered without any interventions.

4.4. Storage and handling

Normally, compounded medicines are prepared for individual patients on an as-needed basis and are dispensed shortly afterwards [1]. However, stocks of compounded medicines can be prepared for future use. Improper storage and handling can cause degradation or contamination and this was the likely cause in one case involving five patients [32].

The issue of storage and handling in compounding is provided in a study conducted in 32 children and adolescents with nephropathic cystinosis who received compounded topical cysteamine 0.55% eye drops over a mean of 4.1 years [33]. The preparation failed to significantly reduce photophobia, despite the fact that, in previous studies, eye drops containing the same or a lower dose of cysteamine demonstrated effectiveness in this indication [33]. The most likely reason for the lack of efficacy of these drops is that cysteamine is a highly unstable active substance and rapidly degrades to inactive cystamine under the influence of light and heat [34,35].

Case reports from both Europe and the USA focused on problems with compounded bevacizumab used in the treatment of ocular conditions. On 25 January 2011, bevacizumab 1.25 mg/50 µL was administered intravitreally to five patients with various ophthalmological conditions at an Italian hospital [32]. The bevacizumab used during these procedures was prepared in 1 mL sterile single-use syringes from commercially available bevacizumab 100 mg/4 mL by an Italian compounding pharmacy on 23

December 2010. Four days after administration of compounded bevacizumab, a 79-year-old patient with neovascular age-related macular degeneration reported blurred vision and floaters in the affected eye. Slit-lamp examination showed the presence of over 50 anterior chamber cells, along with corneal oedema and Descemet's folds, but not hypopyon. Cells and debris were found in the anterior vitreous, while the central vitreous was extremely opaque. Intraretinal haemorrhages were found in the peripheral retina. The patient's visual acuity at this time was 0.2 logMAR, whereas it had been 0.9 logMAR prior to the procedure. Infectious endophthalmitis was suspected and the patient was hospitalised. Vitreous tap was performed. Intravitreal vancomycin 1 mg/100 μL was administered and intravenous treatment with a broad-spectrum antibiotic therapy (piperacillin 2 g and tazobactam 0.25 g three times daily) was initiated. Patients who received compounded bevacizumab from the same batch were contacted and found to also show signs of intraocular inflammation in the injected eyes. Three patients had moderate inflammation which resolved after administration of topical antibiotic-steroid therapy (0.5% levofloxacin plus 0.3% tobramycin and 0.1% dexamethasone four times daily) and intravenous antibiotic therapy (piperacillin 2 g, tazobactam 0.25 g twice daily for 5 days). One patient was prescribed only topical antibiotic-steroid therapy. Vitreous cultures were negative for bacteria and fungi. The patient with severe intraocular inflammation recovered within four weeks, while other patients recovered within two weeks. The compounded bevacizumab did not contain any infectious contaminants or toxins. The authors speculated that the non-infectious endophthalmitis was caused by changes to the immunogenicity of bevacizumab resulting from the storage and handling protocol that was used during compounding. Cases that are simlar to this have also been reported (36).

5. Best practice recommendations

A review of the cases of successful use of compounded medicines, as well as of other relevant sources, has produced a number of best practice recommendations.

At the regulatory level, new provisions of the Food, Drug and Cosmetic Act have been introduced in the USA restricting the use of compounded medicines that are essentially copies of FDA-approved medicines [37].

With regard to preparation or manufacture, the Council of Europe Resolution CM/Res(2016)1 'on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients' recommends that GMP guidelines are applied during the preparation of high-risk compounded medicines, while the Pharmaceutical Inspection Co-operation Scheme (PIC/S) guidelines should be applied in the preparation of low-risk medicines [13]. It is worth noting that this Resolution is advisory and cannot be enforced.

The same resolution provides recommendations on labelling and states that the label should contain the: (a) name, address and telephone number of the dispensing pharmacy; (b) name and address of the preparing pharmacy; (c) name of the pharmacy preparation, if applicable; (d) full qualitative composition and the quantity of the active substance; (e) batch number, if applicable; (f) expiry date or information about limits for use; (g) special storage conditions or handling precautions; (h) directions for use, warnings and precautions; (i) route of administration. However, the case concerning vincristine labelling described above, even when the required information is provided by the compounding pharmacy, labelling errors can still occur.

Several recommendations specific to compounded bevacizumab for use in ophthalmological practice have been made, including preparing all syringes within 6 hours of puncturing the original vial and

discarding any bevacizumab remaining in the vial after this period. It has been reported that, at the Bascom Palmer Eye Institute compounding pharmacy, all bevacizumab syringes are kept in quarantine for 14 days, while 10% of syringes made from each bevacizumab vial undergo microbiological testing. Not a single instance of contamination has been reported after preparation of over 60,000 syringes at that facility [36].

Pharmacists can promote best practices in compounding through professional organisations. The Belgian Association of Pharmacists (APB) has been implementing self-regulation that includes house and hospital pharmacists for several years. Ten times a year, pharmacists receive an invitation to compound various formulations. All samples are collected and analysed for conformity to the European Pharmacopoeia. Every participant receives the general as well as the individual result. And it is welcome to note that few samples exceed the internationally accepted deviations.

6. Discussion

The search for publications reporting issues with compounded medicines in Europe identified 12 case reports/series published between 2003 and 2018. These reports include a total of 26 patients, 11 of them children. This finding was not unexpected, as paediatric patients are some of the most common recipients of compounded medicines [2]. Six of the reports involving a total of 14 patients were from Belgium.

Twenty-four of the 26 patients in these reports made a complete recovery, but two patients experienced permanent sequelae. This includes the case of a woman with multiple sclerosis who received a ten-fold higher than recommended dose of 4-AP due to a compounding error and, as a result, remained encephalopathic at the last follow-up [23]. Similarly, a 42-year-old male patient with a history of spinal cord injury received an overdose of 4-AP [38]. He continued to experience short-term memory loss seven years after the incident [38]. Another case involved a woman who used pharmacy-compounded topical progesterone and oestradiol gels over the course of 28 months and was diagnosed with atypical endometrial hyperplasia [25]. The precise doses contained in the gels were not reported [25]. A 45-year-old male patient, who took a capsule that contained hyoscine hydrobromide instead of hyoscine butylbromide, continued to experience headaches and tremor for up to two years before recovering [21].

The prevalence of problems associated with compounded medicines is difficult to estimate. One reason for this is the lack of data. In many countries, including the USA and European Economic Area, compounding pharmacies are not required to report AEs associated with their products [1,4]. In contrast, manufacturers of licensed medicines are obligated to collect and provide pharmacovigilance information to relevant regulatory bodies [1,4]. Prospective adverse events collection can produce up to double the incidence compared with spontaneous reporting [12]. Another reason is illustrated by the case of pharmacist Robert Courtney, who provided diluted drugs to chemotherapy patients while charging the full price [7]. The scheme went on for nearly 10 years until it [7] was discovered by a pharmaceutical company sales representative who noticed a discrepancy in the amount of drugs Courtney bought and sold [7].

Compounding is widespread in hospital pharmacies, and issues identified in hospitals are likely to be dealt with by robust internal enquiry. Clearly compounding can reduce hospital costs. An example of this is where there is a significant difference in the cost of purchasing a branded version of long acting Fampridine or even a lower cost generic version versus the internally absorbed cost of a compounded version. However, the risks as have been described involving human error and patient harm must not be ignored.

Many problems associated with compounded medicines undoubtedly go unnoticed as patients do not seek medical attention or doctors do not make the connection to the offending product. Therefore, cases included in this report likely represent the tip of the iceberg, vastly underestimating the actual number of cases that occur in clinical practice. Nevertheless, some data on the prevalence of compounding errors are available.

Retrospective analysis of compounding pharmacy records conducted at a children's hospital in France revealed that, in 2010, 14.6% of lots contained non-compliance events, while in 2011, 11.5% contained non-compliance events [39]. Failure of mass and content uniformity tests were the most common reasons for non-compliance [39]. Another study evaluated batches containing one of five active substances prepared at the pharmacy department of the Armand Trousseau hospital in France over 3 years. The proportion of non-compliant lots ranged from 1.0% for ursodeoxycholic acid to 14.8% for morphine hydrochloride [40]. In comparison, FDA-approved medicines fail analytical testing in only 2% of cases [3].

Of all the publications that reported issues with compounded medicines, the rationale for such preparations was provided only in the case of intravitreal bevacizumab [32]. The authors stated that off-label use of bevacizumab was authorised because ranibizumab was not yet approved for some indications, or its use could not be reimbursed [32]. The compounded formulation of bevacizumab used for intravitreal administration caused non-infectious endophthalmitis in all patients who received it, an event presumed to be caused by inappropriate storage and handling [32]. The drugs used in some of the cases described in this report were, at the time, commercially available at the same doses and were approved for the relevant indications [23,24]. However, when no suitable commercial formulation is available, as in two of the five reports of successful use of compounded medicines described here, there is a clear clinical rationale for compounding [15,18]. It is important that approved drugs are used whenever possible in order to ensure patients' safety. In the EU, a product dossier that describes, among other things, the added value of the pharmacy preparation must be provided for high-risk preparations [13].

At present, the primary rationale for compounded medicines is to provide custom pharmaceutical solutions to patients with special needs [1,2]. Examples include patients with allergies to excipients such as palm oil, or children who cannot swallow pills and instead receive liquid oral formulations, etc. However, literature suggests that other factors, such as medicine shortages and budgetary constraints, are significant drivers of compounded medications use [15,41,42]. In the future, development of individualised medicine may become another such factor.

These instances are particularly alarming in light of the fact that the European market for compounded medicines has been projected to grow at a steady pace until 2021 [42].

7. Conclusions

Several case reports/series describing instances of overdose, medication errors and adverse events associated with compounded medications have been published in Europe during the last 15 years. Although the overall number of affected patients was relatively small, many of them were children and two of the adult patients experienced permanent sequelae. The actual number of incidents associated with compounded medicines is unknown, and these numbers should be interpreted with caution. When licensed medicines are available, the use of compounded medicines can put patients at unnecessary risk which should be avoided. Stricter regulation is necessary to prevent similar cases from occurring in the future as the European market for compounded medications grows.

Future recommended actions

1. Stricter regulation is necessary to prevent similar cases from occurring in the future as the European market for compounded medications grows.
2. A comprehensive pan-European survey to gain a greater understanding of compounding procedures and techniques. This would provide valuable information to the benefit of hospital systems and their patients. This should include questions about:
   a. Reasons for compounding
   b. The procedures carried out
   c. Future plans for evolving the scope of compounding
   d. Subcontracting elements
   e. Adherence of good compounding practices and checking systems
   f. Storage stability and durability aspects
   g. Training courses attended
   h. Patient information and communication aspects
   i. Complaints and procedures
   j. Number of individual formulas
   k. Reimbursement procedures
   l. Record keeping processes
3. The results of the survey can then be used to improve the knowledge and quality control of compounded medicines for the good of patient safety.

Acknowledgements

The author would like to thank Georgii Filatov of Springer Healthcare Communications who provided medical writing support in the preparation of this manuscript. This medical writing assistance was funded by The European Confederation of Pharmaceutical Entrepreneurs (EUCOPE).

Author contributions

Mike Isles has read, reviewed and provided guidance on the content of the manuscript.

Conflict of interest

The author has no conflict of interest to report.

Supplementary data

The supplementary files are available to download from http://dx.doi.org/10.3233/JRS-200002.

References

[1] Gudeman J, Jozwiakowski M, Chollet J et al. Potential risks of pharmacy compounding. Drugs R D. 2013;13(1):1–8.
[2] Minghetti P, Pantano D, Gennari CG et al. Regulatory framework of pharmaceutical compounding and actual developments of legislation in Europe. Health Policy. 2014;117(3):328–33.

[3] Mullarkey T. Pharmacy compounding of high-risk level products and patient safety. Am J Health Syst Pharm. 2009;66(17 Suppl 5):S4–13.
[4] Sutherland A, Waldek S. It is time to review how unlicensed medicines are used. Eur J Clin Pharmacol. 2015;71(9):1029–35.
[5] European Parliament. Council of the European Union, Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, 2001.
[6] European Parliament. Council of the European Union, Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, 2004.
[7] Sellers S, Utian WH. Pharmacy compounding primer for physicians: prescriber beware. Drugs. 2012;72(16):2043–50.
[8] Hofer MP, Hedman H, Mavris M et al. Marketing authorisation of orphan medicines in Europe from 2000 to 2013. Drug Discov Today. 2018;23(2):424–33.
[9] European Comission. Safety of medicinal products in the EU. Available from: http://ec.europa.eu/health/human-use/safe_pharma/index_en.htm#. Accessed 8 January, 2019.
[10] Dooms M, Carvalho M. Compounded medication for patients with rare diseases. Orphanet J Rare Dis.13(1):1.
[11] U.S. Food and Drug Administration. Statement from FDA Commissioner Scott Gottlieb, M.D. and Deputy Commissioner Anna Abram on new efforts to assure the quality of compounded drugs. 10 December 2018, 2018. Available from: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm628029.htm. Accessed 9 January, 2019.
[12] EMEA. Evidence of harm from off-label or unlicensed medicines in children. 2004. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500004021.pdf. Accessed July, 2019.
[13] Council of Europe. Resolution CM/Res(2016)1 on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients 2016. Available from: https://www.edqm.eu/sites/default/files/resolution_cm_res_2016_1_quality_and_safety_assurance_requirements_for_medicinal_products_prepared_in_pharmacies.pdf. Accessed 10 December, 2019.
[14] Green DM, Jones AC, Brain KR. Content variability of active drug substance in compounded oral 3,4-diaminopyridine products. J Clin Pharm Ther. 2012;37(1):53–7.
[15] Lannoy D, Cannesson O, Simon N et al. Mepacrine shortage for a giardiase infection resistant to previous treatments: A case-report. In: *44th ESCP International Symposium on Clinical Pharmacy Medicines Information: Making Better Decisions*. 2016; *Int J Clin Pharm*: Lisbon, Portugal, p. 470–598.
[16] Bueno CV, Torres MS, Alonso EM et al. DI-076 Effectiveness and tolerance of dapsone in linear IGA dermatosis in paediatric patients. European Journal of Hospital Pharmacy. 2016;23(Suppl 1):A151–2.
[17] Escoda AC, Genestar JV, Salvador HH et al. DI-042 Trametinib safety and acceptability in paediatric oncology patients: Experience based on a case series. European Journal of Hospital Pharmacy. 2017;24(Suppl 1):A131–2.
[18] Kopsky DJ, Keppel Hesselink JM. Topical phenytoin for the treatment of neuropathic pain. J Pain Res. 2017;10:469–73.
[19] Esquirol-Caussa J, Herrero-Vila E. Human recombinant epidermal growth factor in skin lesions: 77 cases in EPItelizando project. The Journal of Dermatological Treatment. 2018;30:96–101.
[20] Jensen HB, Ravnborg M, Dalgas U et al. 4-Aminopyridine for symptomatic treatment of multiple sclerosis: A systematic review. Ther Adv Neurol Disord. 2014;7(2):97–113.
[21] Van Sassenbroeck DK, Hemelsoet DMR, Vanwalleghem P et al. Three cases of substitution errors leading to hyoscine hydrobromide overdose. Clin Toxicol (Phila). 2005;43(7):861–5.
[22] Genuini M, Freihuber C, Girard I et al. Neonatal intoxication with pyrimethamine: Risk due to the absence of pediatric formulation? *Arch Pediatr*. 2011;18(10):1084–6.
[23] Ballesta Méndez M, van Pesch V, Capron A et al. Seizures and sustained encephalopathy following an accidental 4-aminopyridine overdose XXXIV International Congress of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT). Brussels, Belgium: Taylor & Francis; 2014. p. 318.
[24] Musshoff F, Madea B, Woelfle J et al. Xylometazoline poisoning: A 40-fold nasal overdose caused by a compounding error in 3 children. Forensic Sci Int. 2014;238:e3–5.
[25] Gersak K, Gersak MZ, Dezman LV. Overtreatment with "bioidentical" hormone replacement therapy – a case report. Maturitas. 2015;81(1):148.
[26] Haerden Y, Goossens E, Mostin M. Cluster of naphazoline and phenylephrine intoxications in children due to a compounding pharmacy error XXXV International Congress of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT). St Julian's, Malta: Taylor & Francis; 2015. p. 284–6.
[27] Pirotte B, Stifkens F, Kaye O et al. Hypercalcemia and acute renal failure: A case report of vitamin D intoxication. Rev Med Liege. 2015;70(1):12–6.

[28] Van de Velde K, Siau B, Vermeulen G. Case report: Hyperthermia and diminished consciousness in an elderly woman following an accidental overdose of scopolamine. Acta Neurol Belg. 2015;115(3):517–8.
[29] Hulstaert E, Temmerman L, Van Autryve E et al. Een zeventienjarige jongen met het syndroom van Stevens-Johnson na een marinekamp. Tijdschrift voor Geneeskunde. 2015;71(16):1058–62.
[30] Lorente Fernández L, Belló Crespo M, Santiuste Roman A et al. 5PSQ-095 Likely hypersensivility to 20% autologous serum eye drops. European Journal of Hospital Pharmacy. 2018;25(Suppl 1):A208.
[31] Le Garlantezec P, Aupee O, Almeras D et al. Drug administration error related to computerized prescribing. J Oncol Pharm Pract. 2010;16(4):273–6.
[32] Ricci F, Calabrese A, De Felici C et al. A cluster of presumed, noninfectious endophthalmitis after intravitreal injection of bevacizumab: Long-term follow-up. Digit J Ophthalmol. 2016;22(2):41–5.
[33] Al-Hemidan A, Shoughy SS, Kozak I et al. Efficacy of topical cysteamine in nephropathic cystinosis. Br J Ophthalmol. 2017;101(9):1234–7.
[34] Branko R. Cysteamine eye drops in the treatment of cystinosis – an Australian perspective. Journal of Pharmacy Practice and Research. 2015;45(4):440–5.
[35] Reda A, Van Schepdael A, Adams E et al. Effect of storage conditions on stability of ophthalmological compounded cysteamine eye drops. JIMD Rep. 2018;42:47–51.
[36] U.S. Food and Drug Administration. Compounding policy priorities plan. 2018. Available from: https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm592795.htm. Accessed 12 February, 2019.
[37] Schwam E. Severe accidental overdose of 4-aminopyridine due to a compounding pharmacy error. J Emerg Med. 2011;41(1):51–4.
[38] Trigory L, Ménétré S, May I. Analyse des non-conformités de la fabrication de gélules à doses pédiatriques adaptées et axes d'amélioration. Le Pharmacien Hospitalier et Clinicien. 2013;48(3):182–8.
[39] Mathaut S, Bordenave J, Fratta A et al. Contrôle qualité des préparations hospitalières: Bilan de la productionde gélules d'un hôpital pédiatrique. Annales Pharmaceutiques Françaises. 2006;64(1):44–51.
[40] García MC, Navarro MI, Palacios AS et al. CP-034 Economic impact of the introduction of a compounded 50 mg/ml mercaptopurine suspension in a teaching hospital. European Journal of Hospital Pharmacy. 2016;23(Suppl 1):A15.
[41] Simoens S, Cassiman D, Picavet E et al. Are some orphan drugs for rare diseases too expensive? A study of purchase versus compounding costs. Drugs & Therapy Perspectives. 2011;27(10):24–6.
[42] GlobeNewswire. Compounding pharmacies market is projected to witness stable growth across all global regions due to rising demand for personalized medicines from customers. 2016. Available from: https://globenewswire.com/news-release/2016/02/25/814023/0/en/Compounding-Pharmacies-Market-is-Projected-to-Witness-Stable-Growth-Across-all-Global-Regions-Due-to-Rising-Demand-for-Personalized-Medicines-from-Customers.html. Accessed 29 May, 2018.