

Preparing analgesic infusions – can hospital pharmacies provide quality assurance?

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ABSTRACT

Introduction: This study describes the production of analgesics for infusion pumps in Norwegian hospital pharmacies – what they prepare, how much, and variations between hospital pharmacies and counties.

Study objectives: The current project investigated to what extent infusions of analgesics were prepared in Norwegian hospital pharmacies and if there were any advantages in centralising manufacturing around standardised products.

Method: A structured questionnaire was sent to the 30 hospital pharmacies in Norway. Response rate was 90%. In addition, drug statistics were obtained from the Norwegian Board of Health Supervision.

Results: Twenty-four of the 27 pharmacies that participated had the necessary permission from the authorities to prepare analgesic infusions. The extent to which hospital pharmacies undertook this type of preparation varied greatly, and it was spread out over a large number of drug combinations, strengths and different kinds of packaging. Of the hospital pharmacies, 33% had 83% of the production, and the extent of production at each pharmacy did not seem to depend to any significant extent on the size of the hospital. When patients living at home used analgesic infusions, it was estimated that these were prepared in a hospital pharmacy in 43% of the cases.

Conclusion: As a method of improving the preparative process, infusions of analgesics could profitably be obtained from hospital pharmacies more often. Current production in hospital pharmacies provides few opportunities to standardise and centralise products. However, one should not exclude the possibility of achieving the goals of standardisation and centralisation; they could be achievable if several hospitals agree to use some common routine products whose stability can be proven.

KEYWORDS

Analgesic pumps, home infusion therapy, quality assurance

INTRODUCTION

Medication errors have been the focus of increasing interest in recent years [1]. A review of 73,769 reported errors concerning intravenously-administrated drugs over a five-year period in the US showed that these errors were, in general, more serious than other reported medication errors [2]. Preparing analgesics for infusion involves several risks: the incorrect composition of potent drugs is potentially detrimental to the patient; and infusions given over a long period of time can increase the possibility of microbial growth. The latter is a special cause for concern when the medicines are given by the epidural or intrathecal routes. Some anaesthetists will only recommend epidural solutions prepared in the pharmacy [3].

Analgesic pumps used for palliative cancer treatment, patient controlled analgesia (PCA) used postoperatively and epidural analgesia for women giving birth are examples of analgesics given as infusions. In this paper, the term “analgesic infusions” is used collectively for parenteral infusions with analgesics or local anaesthetics, possibly also in combination with other drugs, for administration by the subcutaneous, intravenous, epidural or intrathecal routes.

The purpose of this study has been to examine to what extent analgesic infusions are prepared in Norwegian hospital pharmacies, and if any of the products could advantageously be standardised and manufactured centrally.

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METHOD

During spring 2004, all Norwegian hospital pharmacies received a structured postal questionnaire, with questions asking how often they manufactured analgesic infusions, routines, and if any specific products were manufactured on a regular basis. Twenty-seven of Norway's 30 hospital pharmacies answered the questionnaire (90%) with copies of the written documentation for all the products manufactured during 12 selected days in 2003 (to optimise the spread of data collection, these 12 days were spread over the year so that each month was represented once, and each week day (except Sunday) twice). The data from the questionnaires and 142 additional documents that were received form the basis of this report.

To get an indication of the total volume of analgesic infusions used by patients staying at home, drug statistics were obtained from the Norwegian Board of Health Supervision. Data were also obtained from the Norwegian Medicines Agency to assess the extent to which private pharmacies manufacture analgesic infusions.

Information essential for evaluating the stability and compatibility of specific drugs was obtained from the *Handbook on Injectable Drugs* [4] and Micromedex [5].

RESULTS

Six of the 27 hospital pharmacies did not manufacture any analgesic infusions during the fourth quarter of 2003; three of these did not have the necessary permission from the Norwegian Medicines Agency. Seventeen hospital pharmacies had permission to manufacture this kind of product for single patients, five met more strict government requirements and could, in addition, manufacture for their own stock; a further two pharmacies could also manufacture and sell from their stock to other pharmacies and medical wholesalers.

Seventeen of the 24 hospital pharmacies who could legally manufacture analgesic infusions stated that they probably had the facilities to increase existing manufacturing to meet demand. However, only six pharmacies had actually made a determined attempt to market this service.

Volume and type of manufacturing

In total, the 27 pharmacies responding to the questionnaire manufactured 2,289 units of analgesic infusions during the fourth quarter of 2003; on the 12 selected days throughout the year, they manufactured 349 units that, when extrapolated to a whole year, suggests just over 9,000 units were manufactured.

The written documentation associated with these products showed that 40% of the units were for either epidural or intrathecal use, and the rest for subcutaneous or intravenous use. Of the products, 55% of the units were delivered to the ward, 12% to patients staying at home, 1% to nursing homes or a hospice, while 21% was manufactured for stock. Data were missing for 9% of the units.

The total of 349 units was made up of 70 different variants, based on differences in strengths and combinations of drugs. Three of these variants made up 50.4% of the total number of units and only a few pharmacies were involved in their manufacture. This significant variation is further compounded by the use of 17 different types and sizes of packaging including infusion bags, syringes, and reservoirs that fitted specific infusion pumps and disposable pumps.

Nine pharmacies routinely manufactured 13 variants of analgesic infusions. These included epidural analgesia for relief during birth, with sufentanil and ropivacaine at three pharmacies, morphine 2 mg/mL at three pharmacies, and ketobemidone 2 mg/mL at two pharmacies. None of the products was identical, because the packaging differed even if the drugs and strengths were the same.

Variations between hospital pharmacies and counties

Table 1 shows the considerable variability in the extent to which pharmacies in university hospitals and other hospitals prepared analgesic infusions. The pharmacy at one university hospital prepared only four such units during the fourth quarter of 2003, while the pharmacy at a smaller hospital within the same health region prepared 209 units during the same period. Altogether, 33% of the pharmacies prepared 83% of the units during this period. During the entire year of 2003, hospital pharmacy estimates of the

Table 1: Statistics about the pharmacies and their production of analgesic infusions

Number of units produced in the fourth quarter of 2003	Number of pharmacies at university hospitals	Number of pharmacies at other (smaller) hospitals
More than 200 units	1	3
101-200 units	3	2
31-100 units	1	3
1-30 units	3	5
0 units	0	6*
Total	8	19

*This number includes three pharmacies without the necessary permission for production.

number of domiciliary patients provided with analgesic infusions averaged 7.7/pharmacy (range: 0-84, median 3).

Statistics from the Norwegian Board of Health Supervision provided data on the number of patients who had been prescribed morphine, ketobemidone, fentanyl or sufentanil (50 mcg/mL) in 5-10 mL ampoules or vials at least once during 2003 (Gunstein Sundene, Norwegian Board of Health Supervision, personal message 31 August 2004). These were used as indicators of the total number of patients staying at home who had used analgesic infusions irrespective of whether or not hospital pharmacies or others were involved in their preparation. These statistics showed that during 2003, 496 patients in Norway, or a mean of 10.9 patients per 100,000 inhabitants, had received such medicines. Differences between counties varied from 6.8 to 20.6 (median 11.9) patients/100,000 inhabitants. As shown in Table 2 there was also a significant variation between the counties in the extent to which analgesic infusions for patients staying at home were prepared by hospital pharmacies. In total, hospital pharmacies were estimated to prepare 43% of all preparations.

The Norwegian Medicines Agency survey of production in Norwegian pharmacies in 2004 showed that 24 of the 30 hospital pharmacies had prepared analgesic infusions during the year, while corresponding numbers for community pharmacies were nine out of 498 (Jørgen Huse, Norwegian Medicines Agency, personal message 13 June 2005). Three of these community pharmacies were in counties where hospital pharmacies had a proportion between 71% and 100%. Two community pharmacies were in counties where hospital pharmacies had a proportion between 0% and 10%, but this means that in four of the counties where hospital pharmacies had a proportion between 0% and 10%, there were no community pharmacies preparing analgesic infusions at all. Consequently, because of their geographic location,

these nine community pharmacies are unlikely to explain the variability reported in Table 2.

Half of the manufactured units contained only one drug, 32% contained a combination of two drugs, while 18% of the units contained a combination of three to five drugs. For the 306 units for which information was made available, the products had expiry dates of five or more days for 254 units, three days for 51 units and one day for one single unit. The *Handbook on injectable drugs* and *Micro-medex* were the most commonly-used reference sources used by hospital pharmacists to judge chemical stability and incompatibilities [4, 5]. The frequency of the drugs used in analgesic infusions together with some information from these two information sources is shown in Table 3.

DISCUSSION

The results show that the preparation of analgesic infusions in Norwegian hospital pharmacies was versatile, and varied greatly in the extent to which such products were prepared within hospital pharmacies.

Bias

The response rate to the questionnaire was very high and the 12 days chosen to obtain detailed information about the products actually prepared was selected in such a way that it would be representative. Because of the low production numbers, information from more than 12 days would, however, have been an advantage.

Calculation of the number of patients receiving analgesic infusions while staying at home is difficult, because it involves substantial uncertainty. Similar uncertainty exists about the proportion prepared by hospital pharmacies within each county. The numbers from the pharmacies are estimates rather than exact figures. The statistics from the Norwegian Board of Health Supervision were based on drugs assumed to be unsuitable for purposes other than infusion, but they are unlikely to represent all analgesic infusions and thus the real number of patients was probably higher. The possibility that some patients could have used the drugs for purposes other than infusion can also not be excluded completely.

Other studies and information

Inevitably, Table 3 gives an incomplete picture of the drugs under study, used either alone or in combination, for analgesic infusions. In comparison, a British study identified 29 different drugs given by infusion via a syringe driver, and 19 of these were used in combination with other drugs [6].

Important reasons for medication errors include unfamiliar procedures and a lack of detailed knowledge in a culture

Table 2: Outpatients using analgesic pumps with hospital-prepared infusions during 2003

Number of counties	Estimated proportion of outpatients for whom hospital pharmacies had prepared the aseptic infusion
3 counties	71% or more
2 counties	41-70%
4 counties	11-40%
6 counties*	0-10%
4 counties	Complete data are lacking

*Three counties without a hospital pharmacy are included.

Table 3: The frequency of specific drugs in the sample of 349 units

Drug	Number of units epid/it	Number of units sc/iv	Affected by light?	pH of the drugs	Known incompatibilities under certain conditions (from the reference sources)
Adrenaline	18	0	Yes	2.2-5	
Bupivacaine	62	0		4-6.5	
Clonidine	24	0		5-7	
Droperidol	0	14	Yes	3-3.8	Ondansetron
Fentanyl	23	3	Yes	4-7.5	Haloperidol
Haloperidol	0	19	Yes	3-3.6	Fentanyl, metoclopramide, midazolam, morphine, ondansetron and sufentanil
Ketamine	1	16	Yes	3.5-5.5	
Ketobemidone	0	147	*	*	*
Metoclopramide	0	9	Yes	3-6.5	Haloperidol
Midazolam	0	15	Yes	About 3	Haloperidol and morphine
Morphine	28	58	Yes	About 5	Midazolam and haloperidol
Ondansetron	0	6	Yes	3.3-4	Droperidol and haloperidol
Ropivacaine	68	0		4-6.5	
Sufentanil	66	7	Yes	3.5-6	Haloperidol

epid: by the epidural route; it: by the intrathecal route; sc: by the subcutaneous route; iv: by the intravenous route; *: information about ketobemidone is lacking in both references. The table includes information from the *Handbook on injectable drugs* [4] or Micromedex [5] that could be important for assessing stability and incompatibility.

that accepts handling of drugs that can be dangerous [7]. Miscalculations are also seen as an important factor [2, 8, 9]. A British study showed many errors connected to the use and handling of parenteral drugs, with an especially high risk associated with multiple-step preparations [10]. A clinical audit, studying 12 cancer patients who had a syringe driver, identified many risk factors regarding lack of routine, and the need for national guidelines [11]. Home infusion practice has several high-risk areas, including complex communication systems, high-risk medication and care in a non-medical setting [12].

Production within Norwegian pharmacies is strictly regulated. Procedures vary because of the manufacturing permission given, but are generally based on good manufacturing practice rules provided by the European Union [13]. Important elements are: trained personnel, a production area separated from other activities, regular control and inspection of aseptic procedures, written hygiene instructions, double-checking and thorough documentation. The use of a laminar air flow bench or an isolator gives a working zone with few particles and micro-organisms.

The Norwegian Medicines Agency has the authority to inspect manufacturing facilities in hospital pharmacies, while the Norwegian Board of Health Supervision has the inspection authority for the rest of the health service. However, there are no detailed quality specifications for aseptic preparation in the wards. This means that potentially hazardous procedures may be essentially uncontrolled and undertaken by staff without specialist pharmaceutical training or experience. In the US, however, the *US Pharmacopoeia* chapter 797 has, since 2004, established practice standards for compounding sterile preparations, with which both pharmacists and other professionals must comply, and which is enforced by regulatory agencies. These standards are differentiated with regard to the extent to which microbial contamination or incorrect composition will be a risk to the patient [14]. Earlier recommendations in the UK allow hospital pharmacies to prepare aseptic products and these have been updated and strengthened in a report from the Audit Commission in 2001 [15]. In addition, in 2001 the Institute of Medicine recommended that high-risk IV solutions should be delivered from the pharmacy already mixed rather than nurses preparing them on the ward or close to the patient [1].

Implications

The preparation of medicines is primarily a pharmaceutical function, but in hospitals other health professionals can be involved; also, whether analgesic infusions are prepared in the pharmacy or by nurses can depend on the anaesthetists' decision. No attempt has been made in this report to evaluate quality differences in aseptic preparation between wards and hospital pharmacies. However, the demands of the various regulating authorities and the competency of pharmacy staff suggest that preparation of infusion products in pharmacies is more likely to guarantee product quality. Economic and practical concerns must be considered, but the variety of practices in Norway indicates that hospital pharmacies could be used far more. An expiry date of five days or more for the majority of the products

provided by the pharmacies also indicates that practical considerations such as product shelf-life are unlikely to be critical. Preparation of analgesic infusions by nurses in primary care can represent an extra risk because of the relative infrequency of this practice by nurses and other non-pharmacy staff.

Reference books can never compensate for professional judgement when several drugs are mixed in the same reservoir, and consulting a pharmacist is recommended. For many drug combinations, laboratory data on compatibility are often missing – different factors can affect how fast drugs deteriorate and the risk of precipitation. Differences in pH between single drugs and the final solutions are particularly important, but also concentration, temperature, diluent and reservoir can have an influence. Many drugs are affected by light and it can be most difficult to determine how much they are affected. Particularly important, however, is avoiding exposure to direct sunlight.

Based on the data herein, it is not possible to state which specific products are suitable for standardisation and centralised production. A survey of what is actually used in analgesic infusions in hospitals can better inform this question. However, it is reasonable to believe that hospitals, as a matter of standard procedure, could use the same type of epidural analgesia for patients giving birth. As long as the product is of sufficient chemical stability, centralised production seems to be a good and effective method to help ensure quality assurance, rather than anaesthetists

or midwives preparing the infusion on the ward. If the criteria for specialist environments and protocols can be agreed for commonly-used products, and the stability is proven for these products, then centralised production could also be suitable for several products within post-operative analgesia. On the other hand, palliative care could be an area where standardisation would be difficult, given that special formulations adjusted to each individual patient are important requirements that need to be met.

CONCLUSION

Quality improvement within health care is complicated and requires many different actions. As a method of improving the preparation process, analgesic infusions could profitably be obtained from hospital pharmacies more often. The pharmacies could, however, market their services better. Cooperation between pharmacists and anaesthetists could make increased standardisation and centralisation of manufacturing possible. Better coordination of government regulations for aseptic preparation in pharmacies and the health service could give a more uniform practice that takes greater advantage of the competencies available.

CONFLICT OF INTEREST

The author is a hospital pharmacist who also had a part-time job as a hospital pharmacist when the project was carried out. However, this project was entirely financed by the School of Pharmacy, University of Oslo, Norway, through his engagement as a PhD student.

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