PARACETAMOL AND IBUPROFEN - ANALGESIC DRUG PRESCRIPTION PATTERNS ON FIVE INTERNATIONAL PAEDIATRIC WARDS

ANALGESIC DRUG USE IN HOSPITALISED CHILDREN

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Key points

- Use of analgesic and anti-inflammatory drugs was in line with local recommendations and WHO guidelines
- Oral paracetamol and oral ibuprofen are the most commonly used analgesic drugs on general paediatric wards
- Differences regarding dose and frequency of ibuprofen and paracetamol use were observed, indicating that safety concerns for individual drugs are perceived differently among countries

ABSTRACT

Aim

Analgesic and anti-inflammatory drugs are frequently prescribed in paediatrics. Prescribing and dosing patterns in hospitalised children are not well known. This study explores analgesic drug utilisation on five paediatric wards and discusses its findings in comparison with WHO guidelines.

Method

A sub-analysis of a prospective, multi-centre, observational cohort study was undertaken. Prescription data of children aged up to ≤18 years were collected between October 2008 and December 2009 on paediatric general medical wards in five hospitals in Australia, Germany, the United Kingdom (UK), Hong Kong (HK) and Malaysia. Analgesic drug prescriptions were analysed for prescribing patterns in terms of dosing, frequency and route of administration. Dosing data were compared with local recommendations and WHO guidelines for children.

Results

In the study cohort 56.8% (726/1,278) of paediatric patients received at least one analgesic drug prescription (1,227 prescriptions). Median age of patients with analgesics was 2.2 years (IQR 0.8-7.3) and median number of prescriptions per patient was 1 (IQR 1-2). Most commonly prescribed drugs were oral paracetamol (45.9%, 563/1,227) and oral ibuprofen (19.9%, 244/1,227). Daily doses of paracetamol ranged from 30 mg/kg/day in Germany to 67-68 mg/kg/day in UK and HK ($p<0.05$). For ibuprofen, single doses ranged from 5-6 mg/kg in HK and UK to 10 mg/kg in GER and AUS ($p<0.001$). Opioid use prevalence was statistically different between the centres and ranged from 0% to 17.6% ($p<0.001$).

Conclusion

This study provides a comprehensive overview of analgesic drug use of hospitalised children. Similar to primary care data, paracetamol is the most commonly used analgesic. As recommended by WHO guidelines, oral medication was favoured and opioids used in addition to paracetamol and ibuprofen. Overall drug utilisation was in line with local recommendations and WHO guidelines. Differences in use of paracetamol and ibuprofen among countries was seen indicating that safety concerns are perceived differently. More large-scale safety studies are needed.

1. INTRODUCTION

Pain management is a key aspect for clinicians in the medical treatment of paediatric patients. Hospitalised children regularly suffer from moderate to severe pain [1-5]. Sadly inadequate pain treatment shown in the 1980s and 1990s is still prevailing [6, 7]. Recent studies estimated that 33-82% of hospitalised neonates, infants and children experience pain during their stay [8-10]. This is worrying as nociception grows with the intensity of the experienced pain [11, 12].

Alongside with several non-pharmacological interventions, analgesic drug use is an important pillar in pain management. Clinicians need profound knowledge in treatment guidelines, drug mechanisms and pharmacological characteristics in children. In order to ensure the best possible pain treatment, the WHO guidelines for pharmacological management of persisting pain in children with medical illnesses outline the cornerstones for this knowledge [13]. Low doses of strong opioid analgesics such as morphine are preferred in addition to baseline analgesia with paracetamol (acetaminophen) or ibuprofen. Finally, analgesic pharmacotherapy should always be tailored to the individual child. In situations with persistent pain, dosing at regular intervals is preferred.

Analgesic and anti-inflammatory drugs are one of the most commonly prescribed drugs for children in primary care and outpatient settings [14, 15]. As one might expect opioid drug prescribing in children is much less common than other analgesics. Furthermore it was shown that opioid selection and prevalence varied largely in an international comparison of primary care data [15].

However, databases used for pharmacoepidemiological studies in primary care infrequently capture drug use in hospitals. Moreover, international and multicentre studies of analgesics use in children in tertiary care settings are largely limited.

We conducted this study to (1) define the prescription and dosing patterns of pain medication in hospitalised children on general paediatric wards in five countries, (2) compare the overall analgesic use with WHO pain guidelines for children, and (3) identify differences in dosing and frequency of use of ibuprofen and paracetamol among countries.

2. METHOD

The findings presented are derived from a sub-analysis of the ADVISE (Adverse Drug Reactions in Children – International Surveillance and Evaluation) study [16]. ADVISE was a prospective, multicentre, observational cohort study conducted on five paediatric general medical wards in Australia (AUS), Germany (GER), Hong Kong (HK), Malaysia (MAL) and the United Kingdom (UK) between 1st October 2008 and 31st December 2009. Demographic data, diagnosis and drug prescriptions of all patients admitted to the study wards during the study period were recorded. Prescription data included drug substance, WHO Anatomical Therapeutic Chemical (ATC) classification, route of administration, dose, unit, frequency, and start and end date. Frequency was classified in two groups: as needed or pro re nata (PRN) and regular dosage regimens. Ethical approval was obtained from each of the local ethics committees prior to data collection (approval references: CA28030 (AUS), 3731 (GER), CRE-2009.474 (HK), NMRR-08-847-2002 (MAL), and 08/H0706/96 (UK)). Further details on the methodology of that study, cohort description and overall drug utilisation are described elsewhere [16-18].

The present study only considers drug prescriptions of the ATC therapeutic main groups N02 (analgesics) and M01 (non-steroidal anti-inflammatory drugs, NSAIDs). Each prescription (combination of drug substance and route of administration) was considered only once per admission. Dosing data was analysed for prescriptions with sufficient information to calculate relative single (e.g. mg/kg) and daily doses (e.g. mg/kg/day). However, this analysis was limited to paracetamol and ibuprofen because prescription data was incomplete for other analgesics or prescription prevalence was too low for meaningful calculations. Results were compared with dose recommendations based on locally used SPCs, dosing guidelines and handbooks [19-23]. Overall analgesic utilisation was additionally compared with guidelines of the WHO [13].

Prescription prevalence was calculated and defined as number of patients with at least one analgesic prescription divided by the total number of patients admitted to the study ward within the study period. Three age groups were formed (≤2 years, 3-11 years and 12-18 years) and all analyses compared between these age groups.

Data analysis was done using statistical software Stata 13 (StataCorp, College Station, Texas, USA). Descriptive statistics are presented as percentages, medians and interquartile ranges (IQR). Chi-squared test and Wilcoxon rank-sum test were used for differences between countries and statistically significant difference was considered at *p*-values <0.05.

3. RESULTS

3.1. Demographics

The total study cohort comprises 5,367 drug prescriptions for 1,278 hospitalised patients. Among those, 1,140 patients received at least one drug prescription. Our analgesic drug utilisation sub-analysis includes 1,227 analgesic prescriptions in 726 patients. Median patient age of that sub-cohort was 2.2 years and the majority of patients (54.7%, 397/726) were below the age of 2 years. Further characteristics of the investigated populations are presented in table 1.

3.2. General analgesic prescription patterns

Analgesic drug prescription prevalence was 22.9% (1,227/5,367) and was highest in UK (26.0%, 522/2,010) closely followed by GER (25.9%, 348/1,343), AUS (19.0%, 143/753), MAL (17.7%, 160/904) and HK (15.1%, 54/357). Nineteen different analgesic drugs and drug combinations were utilised. About half (10/19) of the different drug substances used were opioids.

Median number of analgesic prescriptions per patient was 1 (IQR 1-2). Patients from MAL did not receive more than one analgesic per admission whereas in all other centres patients received up to 5 analgesics (table 1).

The most commonly prescribed analgesic was paracetamol accounting for 54.0% (663/1,227) of prescriptions. In four study centres (AUS, UK, HK, MAL) oral paracetamol was the most commonly prescribed analgesic (47.7-95.6%). In contrast, oral ibuprofen (33.3%, 116/348) followed by parenteral metamizole (28.4%, 99/348) were most frequently prescribed in GER.

An overview of the overall analgesic drug prescription pattern and exposure rates in all five centres is presented in table 2.

3.3. Routes of administration

Oral administration of analgesics was by far the preferred route of administration in all centres (77.0%, 945/1,227), especially in MAL (98.1%, 157/160), figure 1. In GER oral administration was less common (50.9%, 177/348) in favour of parenteral administration (31.5%, 110/348). Metamizole intermittent infusions accounted mostly for that. Other centres used intermittent infusions as parenteral route of administration in 1.9-14.0% of prescriptions. The rectal route of administration was rarely used, except for GER where 17.5% (61/348) of prescriptions were administered rectally, mainly paracetamol suppositories. Nasal and topical administration of analgesics was seen in UK but only in single cases (<1.0%).

Route of administration distribution was similar in all three age groups except for the rectal route. As expected, this route was most frequently used in children ≤2 years (8.2%, 48/586 of analgesic prescriptions in that age group) and least common in patients aged 12-18 years (0.5%, 1/208).

3.4. Dosing frequency

Most of the analgesics (69.1%, 848/1,227) were prescribed PRN. This was the case in GER (88.5%, 308/348), MAL (82.5%, 132/160), AUS (78.3%, 112/143) and UK (55.6%, 290/522). However, in HK, most analgesic prescriptions were regularly prescribed dosage regimens (90.7%, 49/54).

3.5. Paracetamol

The most commonly prescribed analgesic in AUS, UK, HK and MAL was oral paracetamol. To identify potential differences between countries we further investigated the prescribed oral single doses and compared them with local recommendations. The median single dose ranged from 11 mg/kg in HK to 16 mg/kg in the UK ($p<0.001$) where the maximum single dose was as high as 20 mg/kg (figure 2).

Daily doses in fixed dosage regimens ranged from 30 mg/kg/day in GER to 67-68 mg/kg/day in UK and HK ($p<0.05$) where maximum daily doses above 75 mg/kg/day were seen. Nevertheless, paracetamol was prescribed most often as needed (73.3%, 486/663). We compared median oral and rectal single doses in GER, but no significant difference was found (both 13.9 mg/kg, $p=0.708$).

When used in fixed dosage regimens, most centres administered it four times per day. In contrast, the median paracetamol dosing frequency was six times daily in HK. The dosing pattern was not significantly different in the three age groups.

3.6. Ibuprofen

Being the second most frequently used analgesic drug, we also investigated the dosing pattern of oral ibuprofen. Rectal route was only used in single cases and only in GER. Single doses ranged from 5-6 mg/kg in HK and UK to 10 mg/kg in GER and AUS ($p<0.001$). Median daily doses ranged from 19 to 30 mg/kg/day and were rather similar (figure 3).

Analogous to paracetamol, ibuprofen single and daily doses were mostly in agreement with recommended dose ranges.

However, in GER single doses above the recommendation limit of 10 mg/kg were used in some cases. Ibuprofen was also commonly given as needed (73.4%, 182/248), but in case of regularly prescribed

dosage regimens the median frequencies were 2-3 times per day. The dosing profile was not significantly different in the three age groups.

3.7. Combined Paracetamol and Ibuprofen Use

Paracetamol and ibuprofen were regularly prescribed in an alternating dosing regimen in UK, GER and AUS (figure 4). In these centres, 41.3%, 32.9% and 14.0%, respectively, of patients with at least one prescription of these drugs were prescribed with a concurrent combination of both drugs. Yet, paracetamol monotherapy was predominant in all centres except GER. However, if ibuprofen was prescribed, GER was the only centre using it in monotherapy at a larger scale. All other centres used ibuprofen mainly in an alternating regimen with paracetamol (figure 4).

3.8. Opioids

10.8% (133/1,227) of all prescriptions were an opioid drug and 12.0% (87/726) of all patients with at least one analgesic prescription received an opioid. Morphine was the most frequently used opioid drug, however, only in AUS and UK. Other opioids such as tramadol, codeine or pethidine were prescribed less often. In the study centres in GER, HK, AUS and UK, the opioid exposure in patients with analgesics was 4.5% (8/177), 14.6% (6/41), 18.9% (18/95) and 21.6% (55/255), respectively ($p<0.001$). In MAL only non-opioid analgesics were prescribed. Opioid drug exposures of the complete study cohorts are presented in table 2. We did not find significant prescribing differences in the three age groups at each studied centre.

We further investigated whether patients with opioids were also concomitantly receiving non-opioid drugs, e.g. paracetamol or ibuprofen. Most patients (95.4%, 83/87) with at least one opioid drug also received at least one non-opioid analgesic – mainly paracetamol or ibuprofen (94.3%, 82/87). Opioids were administered equally via oral or parenteral route with prevalence 49.6% (66/133) each. Additionally, one single patient from UK received nasal diamorphine.

3.9. Other analgesic drugs

Other analgesics with exposure >1% were clonidine, diclofenac, metamizole and tramadol. These analgesics were only seen at particular centres, e.g. clonidine and diclofenac were limited to UK and metamizole to GER due to its restricted availability status in other countries. Tramadol use was only observed in AUS, GER and HK.

4. DISCUSSION

This is one of the first multi-national analgesic drug utilisation studies in hospitalised children. The study was designed to consistently collect prescription data of children admitted to paediatric general medical wards. This allowed us to conduct a comprehensive comparison of the analgesic drug prescription patterns of five paediatric hospitals in Australia, Germany, United Kingdom, Hong Kong and Malaysia.

Recent WHO guidelines for analgesic use in children recommend the key concept of the two-step strategy using non-opioid drugs and potent opioid drugs [13]. As recommended by the WHO, paracetamol and ibuprofen are first-line therapy for mild pain. Single centre studies showed that paracetamol and NSAIDs such as ibuprofen are most commonly used in pyrexia and mild to moderate

pain in hospitalised children [10, 24]. We can confirm this first-line approach in our five cohorts with paracetamol and ibuprofen being the most frequently used analgesics.

Paracetamol was the most commonly prescribed drug in all centres but GER. Highest doses were used in UK whereas in GER doses were well below those in other countries. During the time of data collection, recommendations for maximum daily doses of paracetamol ranged from 60 mg/kg/day (GER, AUS) up to 90 mg/kg/day (UK) for severe symptoms which may explain the observed differences.

In addition, reasons for the limited use of paracetamol in GER could be recent concerns and public discussions about the safety of paracetamol and its risks for hepatotoxicity [25]. At that time, the maximum quantity of paracetamol per package that can be purchased over-the-counter was limited in Germany and partially put under prescription-only medicine due to those discussions [26].

In the UK safety concerns around paracetamol arrived later. The BNF for Children recommendation for paracetamol was lowered from 90 mg/kg/day to 75 mg/kg/day (max. 4 g per day) in 2011 only after reports of paracetamol toxicity with doses between 75-150 mg/kg/day and thus are not reflected in our study yet [27].

Nevertheless, it must be acknowledged that paracetamol seems to be reasonably safe when used within the dosing recommendations and when measures have been taken to prevent medication errors or accidental overdosing [28]. Furthermore, in order to achieve concentrations effective for analgesia at least standard doses are needed. These can be achieved by intravenous and oral route of administration. Therefore an overstated caution of paracetamol use may put paediatric patients at risk for inadequate analgesia due to underdosing. In contrast, concentrations obtainable by the rectal route at standard doses are sufficient for antipyresis only [28]. Higher target concentrations would require much higher and potentially toxic doses. Consequently, rectal paracetamol is not recommended, especially for pain relief.

In our study we did not observe dosing differences between the oral and the rectal at our centre in Germany. However, because there is no link to the indications we do not know whether the rectal route of administration was used for antipyresis only.

In contrast to paracetamol the popularity of ibuprofen and the availability of paediatric ibuprofen formulations increased since the late nineties. A meta-analysis has shown that in children, single doses of ibuprofen (4-10 mg/kg) and paracetamol (7-15 mg/kg) have similar efficacy for relieving moderate to severe pain, and similar safety as analgesics or antipyretics. Ibuprofen (5-10 mg/kg) was a more effective antipyretic than paracetamol (10-15 mg/kg) [29].

Due to the increasing concerns of paracetamol particularly in Germany and the increasing popularity of ibuprofen, the German centre favoured ibuprofen and even used single ibuprofen doses slightly exceeding the recommendations.

Interestingly, there is agreement in local recommendations regarding ibuprofen dosing which was not the case for paracetamol. Only maximum daily doses for ibuprofen in AUS and MAL were slightly higher than in the other three countries. These differences among countries indicate that safety concerns are perceived differently and drugs with longer experiences such as with paracetamol are favoured over younger drugs even though no differences in the safety profile have been shown [29].

Alternating dosing regimens using paracetamol and ibuprofen were regularly used in UK, GER and AUS, but not in HK and MAL. Interestingly, ibuprofen generally does not play a major role in the latter two centres. GER was the only centre using ibuprofen both in alternating combination with paracetamol and in monotherapy. This needs to be reviewed carefully as data on safety and efficacy of alternating combined therapy in children with pain is lacking [28, 30]. A systematic review concluded that the safety and efficacy of the combination of ibuprofen and paracetamol in fever remains obscure [31] and there may be an additional risk for medication errors [32].

Metamizole was the second most frequently prescribed analgesic in GER whereas none of the other centres used this drug. It is popular for its additional spasmolytic properties and use in visceral pain [33]. However, it is unlicensed in most countries for its association with life-threatening agranulocytosis although the extent of this risk remains controversial [34-36].

Most analgesics were prescribed without regular intervals unlike endorsed by WHO guidelines [13]. A reason for that could be that pain was not persistent in most patients. Most of our patients received analgesic drugs by oral route of administration in agreement with the WHO.

We furthermore investigated the opioid drug prescription patterns. In 12% of the patients receiving analgesics, at least one opioid was prescribed. Almost all of these patients received a combination of an opioid and non-opioid drug as advocated by the WHO guidelines. Less recommended drugs such as codeine, tramadol or pethidine were infrequently used. This is in line with the WHO guideline which removed intermediate potency opioids such as codeine or tramadol as an additional step due to individual biotransformation variability and missing data on effectiveness and safety in children.

Prevalence of opioid use was significantly different between the studied centres. In MAL only non-opioids were used and in GER only 4.5% of patients with analgesics received an opioid. However, as for GER, opioids are regularly used in the paediatric intensive care unit and on the paediatric oncology ward. Nevertheless, opioid use was more common on paediatric general medical wards in the remaining centres with frequencies between 14.6-21.6%. One reason for this observation could be that the studied patients in UK and AUS were admitted with more painful conditions [16, 18]. Other reasons may be greater fear of opioid use, e.g. due to opioid-induced adverse effects, inadequate drug availability, local policies and regulations obstructing opioid analgesics accessibility or different analgesic requirements of the studied patients [13, 24, 37].

Since our data origin from 2008/2009 they may not represent latest clinical practice. The EU Paediatric Regulation came into force in 2007 and there has been a considerable advancement in paediatric drug research. Risks are being assessed more comprehensively and new data on the safety and efficacy become available. In 2013, for instance, the European Medicine Agency (EMA) prohibited the use of medicines containing codeine for patients under the age of 12 years and put further specific restrictions on its use. On the other hand, evidence became available that tramadol may be a valid alternative requiring attention only for a subset of patients [38]. Paediatric studies on newer, medium potent opioids such as tapentadol are ongoing within the frame of a paediatric investigation plan (PIP) and results may become available in the near future [39, 40]. Also more data regarding the benefits and risks of paracetamol, ibuprofen and its combinations became available and may influence practice [31]. Therefore, our data form an excellent basis to evaluate the impact of these latest regulatory developments and to compare the effectiveness of changes in guidelines and recommendations.

There are a few limitations of our investigation. One may be the restricted generalisability due to the small scale study design and the fact that each country was only represented by one ward. However, all hospitals were university hospitals, study wards were specialised in general paediatrics and we have applied a standardised data collection method directly on ward which makes the multi-centre comparisons possible.

Since we do not know the indication for each drug prescription, it was not possible for us to include analgesic drugs from other ATC classes such as antiepileptics (e.g. gabapentin), antidepressants (e.g. amitriptyline) or local anaesthetics (e.g. lidocaine). Additionally, as we investigated the analgesics utilisation on paediatric general medical wards, our patients mostly suffered from acute pain and thus conclusions cannot be drawn for the treatment of chronic pain in children. We were also not able to distinguish whether the drug was truly administered to the patient or not, because the study only recorded the prescriptions from the medical charts. Similarly, it was also not possible to reasonably calculate the daily dose for many prescriptions because either they were prescribed as needed without a maximum daily frequency, actual number of daily administrations or drug concentration was not available (e.g. ibuprofen syrups or morphine infusion solution). For the reasons mentioned, we limited our dosing analysis to paracetamol and ibuprofen. Finally, we were not able to investigate the suitability of drug regimens for the patients' conditions and whether patients were appropriately treated in relation to pain severity.

5. CONCLUSION

This study provides a comprehensive picture of prescription patterns of the analgesic drugs used in hospitalised children in five international hospitals. More than every second child received at least one analgesic drug during their hospital stay. Overall analgesic treatment was in line with the WHO guidelines with paracetamol and ibuprofen being the most important analgesics. Yet, differences were observed in the individual use of these two drugs. Safety concerns seem to be perceived differently indicating that large-scale safety studies are missing.

The most commonly used opioid drug was morphine, intermediate potency opioids such as codeine or tramadol are used rarely showing the changes in the WHO scheme were implemented across the world.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest

SB, AR, IW, ST and AN have declared that they have no financial interests that may be relevant to the submitted work.

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Ethical Approval & Informed Consent
The study protocol was reviewed and approved by the appropriate national research ethics committee in each participating country and has been performed in accordance with the ethical standards of the Declaration of Helsinki. As this was an observational study, involving intensive chart review, no direct contact with patients or informed consent was required. Only anonymised data was recorded which cannot be traced to individual patients.

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TABLES

Table 1: Demographics of the analgesic sub-cohort (patients with at least one analgesic prescription)

Patient characteristics	AUS (N=95)	GER (N=177)	UK (N=255)	HK (N=41)	MAL (N=158)	TOTAL (N=726)
Age (years, median, IQR)	1.9 (0.7-7.3)	4.0 (1.0-10.5)	2.3 (0.9-8.2)	5.6 (1.7-15.1)	1.1 (0.6-2.6)	2.2 (0.8-7.3)
≤2 years (n, %)	56 (58.9)	66 (37.3)	138 (54.1)	14 (34.1)	123 (77.8)	397 (54.7)
3-11 years (n, %)	30 (31.6)	70 (39.5)	85 (33.3)	13 (31.7)	35 (22.2)	233 (32.1)
12-18 years (n, %)	9 (9.5)	41 (23.2)	32 (12.5)	14 (34.1)	0	96 (13.2)
Gender (male, n, %)	52 (54.7)	100 (56.5)	138 (54.1)	23 (56.1)	85 (53.8)	398 (54.9)
Length of stay (days, median, IQR)	5 (3-7)	4.5 (3-7)	4 (3-6)	5 (4-7)	6 (4-9)	5 (3-7)
Total no. of analgesic prescriptions	143	348	522	54	160	1,227
Analgesic prescriptions per patient (median, IQR, max)	1 (1-2, 5)	2 (1-2, 5)	2 (1-2, 5)	1 (1-1,5)	1 (1-1, 1)	1 (1-2, 5)

IQR: interquartile range.

Table 2: Numbers and exposure rates of prescribed analgesics per site and the full ADVISE study cohort

Drug	ATC Code	Route	AUS (N=146)	GER (N=376)	UK (N=313)	HK (N=143)	MAL (N=300)	TOTAL (N=1,278)
Acetylsalicylic acid	N02BA01	Oral			1 (0.3)		2 (0.7)	3 (0.2)
Buprenorphine	N02AE01	Parenteral		1 (0.3)				1 (0.1)
Choline salicylate	N02BA03	Topical			3 (1.0)			3 (0.2)
Clonidine	N02CX02	Oral			22 (7.0)			22 (1.7)
		Parenteral			6 (1.9)			6 (0.5)
Codeine, comb.	N02AA59	Oral	3 (2.1)		2 (0.6)	5 (3.5)		10 (0.8)
Diamorphine	N02AA09	Nasal			1 (0.3)			1 (0.1)
Diclofenac	M01AB05	Oral			20 (6.4)			20 (1.6)
		Rectal			3 (1.0)			3 (0.2)
Fentanyl	N02AB03	Parenteral	1 (0.7)		5 (1.6)			6 (0.5)
Ibuprofen	M01AE01	Oral	16 (11.0)	116 (30.9)	108 (34.5)	2 (1.4)	2 (0.7)	244 (19.1)
		Rectal		4 (1.1)				4 (0.3)
Metamizole	N02BB02	Oral		18 (4.8)				18 (1.4)
		Parenteral		99 (26.3)				99 (7.7)
Morphine	N02AA01	Oral			39 (12.5)			39 (3.1)
		Parenteral	12 (8.2)		36 (11.5)			48 (3.8)
Naproxen	M01AE02	Oral	1 (0.7)			1 (0.7)		2 (0.2)
Oxycodone	N02AA05	Oral	7 (4.8)					7 (0.5)
Paracetamol	N02BE01	Oral	88 (60.3)	40 (10.6)	249 (79.6)	33 (23.1)	153 (51.0)	563 (44.1)
		Parenteral	5 (3.4)	4 (1.1)	24 (7.7)		3 (1.0)	36 (2.8)
		Rectal	2 (1.4)	57 (15.2)	3 (1.0)	2 (1.4)		64 (5.0)
Paracetamol, comb.	N02BE51	Oral				7 (4.9)		7 (0.5)
Pethidine	N02AB02	Parenteral				3 (2.1)		3 (0.2)
Piritramide	N02AC03	Parenteral		2 (0.5)				2 (0.2)
Tilidine	N02AX01	Oral		1 (0.3)				1 (0.1)
Tramadol	N02AX02	Oral	6 (4.1)	2 (0.5)		1 (0.7)		9 (0.7)
		Parenteral	2 (1.4)	4 (1.1)				6 (0.5)
Any non-opioid drug	**M01/N02 excl. N02A**	**Any**	**92 (63.0)**	**177 (47.1)**	**254 (81.2)**	**41 (28.7)**	**158 (52.7)**	**722 (56.5)**
Any opioid drug	**N02A**	**Any**	**18 (12.3)**	**8 (2.1)**	**55 (17.6)**	**6 (4.2)**	**0 (0)**	**87 (6.8)**
Any NSAID	**M01A**	**Any**	**16 (11.0)**	**117 (31.1)**	**115 (36.7)**	**2 (1.4)**	**2 (0.7)**	**252 (19.7)**
Any analgesic drug	**M01/N02**	**Any**	**95 (65.1)**	**177 (47.1)**	**255 (81.5)**	**41 (28.7)**	**158 (52.7)**	**726 (56.8)**

Number of patients with at least one drug prescription (drug exposure in %, number of patients with at least one prescription by total number of admitted patients on each ward). Total number of analgesic prescriptions n=1,227. NSAID: Nonsteroidal anti-inflammatory drug.

FIGURES

Figure 1: Proportion of analgesic prescriptions by route of administration (in percent, *n* Number of prescriptions)

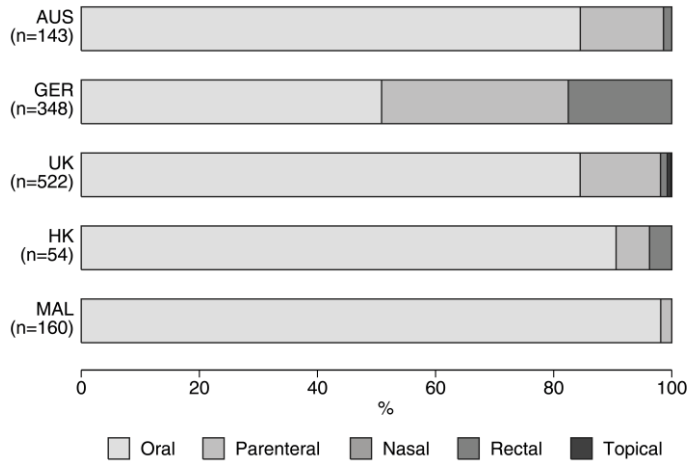

Figure 2: Oral paracetamol single (mg/kg, median, interquartile range) and daily doses (mg/kg/day, median, interquartile range; only regularly prescribed dosage regimens) compared with local dosing recommendation (AUS [19], GER [20], UK [21], HK [21, 22] , MAL [22], *n* number of prescriptions)

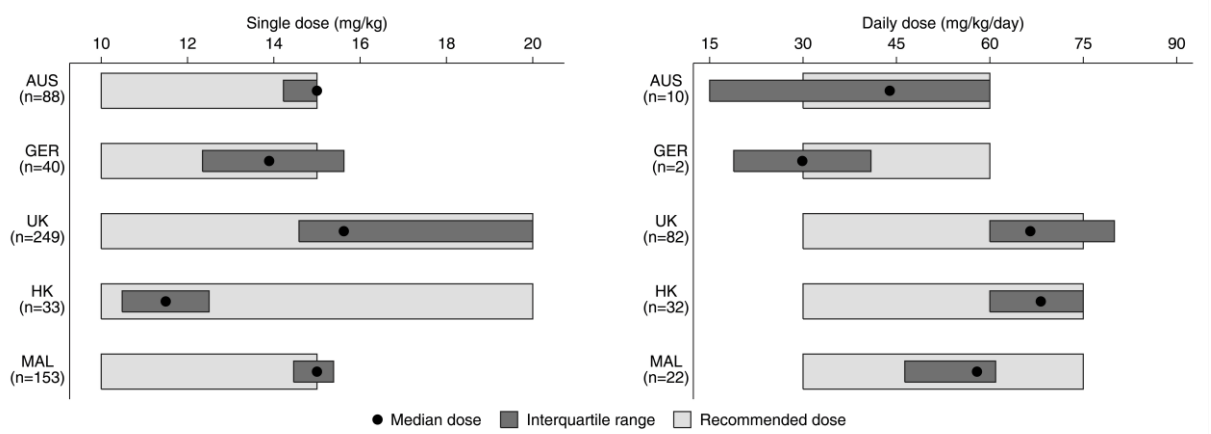

Figure 3: Oral ibuprofen single (mg/kg, median, interquartile range) and daily doses (mg/kg/day, median, interquartile range; only regularly prescribed dosage regimens) compared with local dosing recommendation (AUS [19], GER [23], UK [21], HK [21, 22], MAL [22], *n* number of prescriptions)

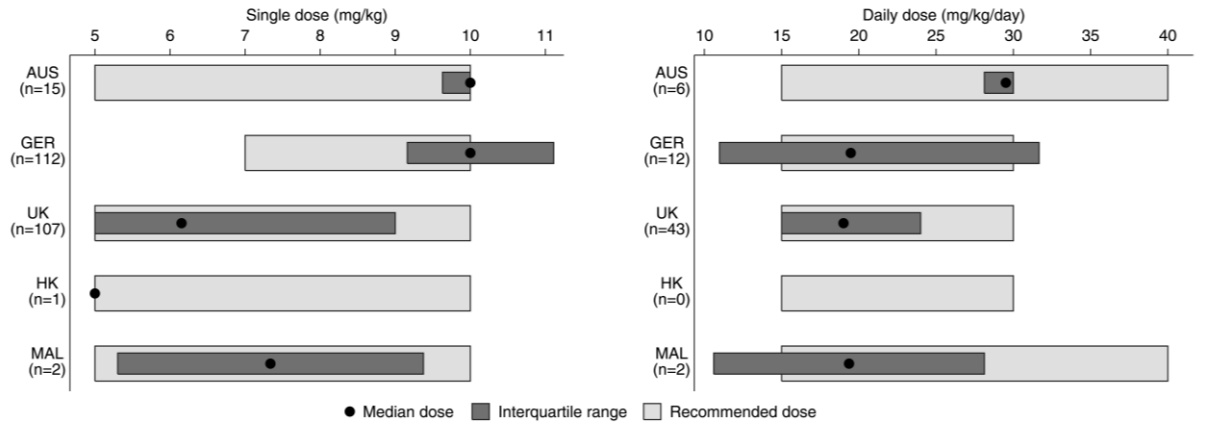

Figure 4: Proportion of patients with either paracetamol monotherapy, ibuprofen monotherapy or combined prescription (percent, *n* number of patients)