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Paediatric hospitalisation related to medications administration errors of non-opioid analgesics, antipyretics and antirheumatics in England and Wales: a longitudinal ecological study

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ABSTRACT

Objective This study aimed to explore paediatric hospitalisation related to medication administration errors (MAEs) of non-opioid analgesics, antipyretics and antirheumatics in England and Wales.

Design An ecological study.

Setting A population-based study on hospitalised patients in England and Wales. Hospital admission data were extracted from the Hospital Episode Statistics database in England and the Patient Episode Database for Wales for the period between April 1999 and April 2020. Admissions cause was confirmed using the diagnostic codes T39.0–T39.9.

Participants Paediatric patients aged 15 years and below who were hospitalised at all National Health Service (NHS) trusts and any independent sector funded by NHS trusts.

Primary outcome measure Hospitalisation rates related to MAEs of non-opioid analgesics, antipyretics and antirheumatics.

Results The yearly number of admissions for MAEs associated with non-opioid analgesics, antipyretics and antirheumatics experienced a notable growth of 21.7% over the span of two decades, rising from 4574 cases in 1999 to 5568 cases in 2020. The observed increase demonstrates a significant upward trend in hospital admissions rate, with a 12.3% growth from 46.16 per 100 000 individuals in 1999 to 51.83 per 100 000 individuals in 2020 (95% CIs 44.83 to 47.50 and 50.47 to53.19, respectively, trend test, p<0.05). The therapeutic categories that exhibited the highest frequency of MAEs were '4-aminophenol derivatives' and 'other non-steroidal anti-inflammatory drugs', accounting for 79.3% and 16.0% of cases, respectively. It is worth noting that there was a significant increase of 28.9% in hospitalisations linked to MAEs specifically associated with '4-aminophenol derivatives.'

Conclusion The research revealed a notable rise in the overall yearly number of hospital admissions associated with MAEs within the paediatric population. This study emphasises the necessity for additional research aimed at mitigating the potential hazards associated with the ingestion of these medications, particularly within susceptible demographics, such as young children.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study investigated the hospitalisation patterns associated with medication administration errors of non-opioid analgesics, antipyretics and antirheumatics in paediatric patients from 1999 to 2020.
⇒ Conducting ecological studies related to hospitalisation patterns among the paediatric population is important in identifying research questions that warrant further investigation and research.
⇒ The utilisation of population-level aggregated data might overestimate or underestimate the presented hospitalisation rates.
⇒ The utilisation of population-level aggregated data precluded our ability to conduct follow-up assessments on paediatric patients or identify significant confounding variables.
⇒ The utilisation of aggregated data posed limitations on the capacity to access pertinent demographic information of paediatric patients, including comorbidities and ethnicity.

INTRODUCTION

Globally, the rate of poisoning with over-the-counter (OTC) drugs and prescription drugs is steadily increasing, as medication administration errors (MAEs) are considered a medical emergency expressing a leading health issue.[1 2] The term 'medication error' is used to describe any mistake that occurs during the process of prescribing, dispensing or administering medication. The term MAE refers to any discrepancy that occurs when comparing the actual medication received by a patient to what was intended by the prescribing physician at the time the order was placed.[3] MAE occurs when there is a discrepancy between the medication consumed by the patient and the intended pharmacological therapy.[4] The International Statistical Classification of Diseases and Related Health Problems (ICD) system categorises MAEs as

incidents of poisoning, adverse effects or underdosing of drugs.[5]

Worldwide, the most used medications are analgesics, and analgesic use has been regularly rising throughout the past years.[6 7] The 2020 American Association of Poison Control Centers (AAPCC) Annual Report concluded that, in all human exposures, analgesics were the most common reason for drug poisoning.[8] Analgesics are used to manage pain (chronic, acute, severe, moderate and mild).[9] Typically, non-opioid and opioid medications are used for analgesia.[9] According to the 2020 AAPCC Annual Report, acetaminophen is among the leading reasons for analgesic poisoning.[8] Acetaminophen is a non-opioid analgesic with antipyretic and analgesic effects,[10] present in hundreds of OTC and prescription medications.[11] Acetaminophen poisoning usually causes hepatotoxicity (liver failure, liver damage) or even mortality.[12]

When more than one drug is taken, poisoning can induce more severe consequences.[8] That is because of drug–drug interactions, pharmacodynamics and pharmacokinetics.[12] In the USA, drug-related problems result in 8.7 million hospital admissions and 17 million emergency department visits annually.[13] In the USA, more than 1 million emergency department visits occur annually due to drug-related overdose.[14] In Victoria (Australia), 47% of drug-related hospital admissions were because of drug poisoning in 2019–2020.[15] Age-standardised drug-related hospital admissions rates for non-opioid analgesics were 24 per 100 000 individuals (95% CI 22.7 to 25.1) in Victoria (Australia).[15]

In the UK, the most common type of poisoning is medicine overdoses,[16] and the most common drugs or medicines that cause poisoning include paracetamol and aspirin.[17] In England and Wales, there were 4561 deaths related to medication poisoning in 2020 (3.8% more increased than the number of deaths in England and Wales in 2019), representing a deaths rate of 79.5 per million individuals.[18] Moreover, drug-related poisoning rates increased by 60.9% (from 49.4 per million in 2010 to 79.5 deaths per million in 2020). Since 2012, drug-related poisoning rates have increased every year.[18]

There exist several factors that render the paediatric population more vulnerable to medication errors and subsequent complications arising from medication administration. These factors encompass the presence of diverse dosage forms of a given medication, incorrect dosing, absence of standardised dosing regimen and the level of maturity in organ systems.[19] Accordingly, this research aimed to explore paediatric hospitalisation related to MAEs of non-opioid analgesics, antipyretics and antirheumatics in England and Wales.

METHODS

Study sources and the population

This was a descriptive longitudinal ecological study using publicly available data extracted from the Hospital Episode Statistics (HES) database in England and the Patient Episode Database for Wales (PEDW) for the period between April 1999 and April 2020.[20 21] The HES database is a valid and reliable source for research purposes.[22] The data entry and quality checks are monitored and improved regularly.[23] The HES data are collected from clinical notes and discharge summaries.[24] Trained clinical coders at each trust are responsible for entering the data, adhering to a national data standard. A limited number of cases are subject to annual audits where data from the HES is compared with clinical audits.[24] The data are systematically gathered and encoded at each individual facility.[21] The records are thereafter electronically transmitted to Digital Healthcare in Wales, where they undergo validation and integration into the primary database.[21]

The HES and PEDW databases contain hospital admission data related to MAEs (accidental (unintentional), intentional self-harm or assault) for paediatric patients (aged 15 years and below). We identified MAEs hospitalisation using the 10th Revision of the ICD 5th Edition (used by National Health Service to classify diseases and other health conditions) (T39.0–T39.9). HES and PEDW data are checked regularly to ensure their validity and accuracy. To calculate the yearly paediatric hospital admission rate, we collected the paediatric midyear population data for the period between 1999 and 2020 from the Office for National Statistics.[25]

Statistical analysis

Hospital admission rates with 95% CIs were calculated using the finished consultant episodes divided by the midyear paediatric population. We used the χ^2 test to assess the difference between the hospital admission rates between 1999 and 2020. The trend in hospital admissions was assessed using a Poisson model. The CI was estimated using the following equation for the population proportion: $p\hat{}+/-z^* (p\hat{}(1-p\hat{})/n)^{0.5}$. All analyses were conducted by using SPSS V.27 (IBM).

Patient and public involvement

None.

RESULTS

The annual number of admissions for MAEs involving non-opioid analgesics, antipyretics and antirheumatics increased by 21.7% from 4574 in 1999 to 5568 in 2020. This increase indicates a rise in the rate of hospital admissions by 12.3% (from 46.16 per 100 000 persons in 1999 to 51.83 per 100 000 persons in 2020, with 95% CIs 44.83 to 47.50 and 50.47 to 53.19, respectively, trend test, p<0.05).

The therapeutic classes that were most frequently associated with MAEs were '4-aminophenol derivatives' and 'other non-steroidal anti-inflammatory drugs (NSAID),' comprising 79.3% and 16.0%, respectively (table 1).

Over the course of the study period, there was a notable 28.9% rise in hospitalisations associated with MAEs related to'4-aminophenol derivatives'. However, there was a significant decrease in hospitalisation rates

Table 1 Percentage from total number of admissions

Diagnostic code	Therapeutic class of the medications that caused medication administration error	Percentage from total number
T39.0	Salicylates	3.3
T39.1	4-aminophenol derivatives	79.3
T39.2	Pyrazolone derivatives	0.1
T39.3	Non-steroidal anti-inflammatory drugs (propionic acid derivatives)	16.0
T39.4	Antirheumatics	0.1
T39.8	Other non-opioid analgesics and antipyretics	0.9
T39.9	Non-opioid analgesic, antipyretic and antirheumatic, unspecified	0.4

associated with MAEs related to 'non-opioid analgesics, antipyretics and antirheumatics,' 'other non-opioid analgesics and antipyretics, not elsewhere classified,' 'pyrazolone derivatives,'salicylates and NSAIDs. The decrease in hospitalisation rates for these categories was 100.0%, 85.9%, 84.6%, 67.8% and 5.4% respectively, as shown in table 2 and figure 1.

DISCUSSION

Analgesics are on the top of the most common OTC prescriptions prescribed in UK and considered one of the most common causes of self-poisoning.[26] This study aimed to explore the trend of paediatric hospital admissions related to MAEs of non-opioid analgesics, antipyretics and antirheumatics in England and Wales.

This study found that the total annual number of hospital admissions related to MAEs of non-opioid analgesics, antipyretics and antirheumatics for various reasons increased by 21.7% during the study period between 1999 and 2020, expressing an increase in the hospital admission rate of 12.3%. This is confirming the findings of a previous study by Naser *et al*, which reported that the prescribing rate for analgesics increased by 21.9% for analgesic medicaitons for the duration between 2004 and 2019.[27] In addition, other investigations conducted in Denmark, Sweden and Norway have examined the utilisation patterns of many categories of drugs, including opioids and antiarrhythmic medications, and have documented a rise in their utilisation.[28–30] This seems reasonable due to the massive increase of the usage of analgesics in the recent decade.[31] This increase is in line with the increase of admissions to hospitals related to MAEs by non-opioid analgesics, antipyretics and antirheumatics in the Lower Silesia region of Poland in the years 2006–2012.[32] This increase could be related to the increase of the usage of OTC medications that leads to increase the availability of these medications, which increases the risk of deliberate or accidental overdose. Meanwhile, the increase rate of hospital admission due to poisoning of non-opioid analgesics, antipyretics and antirheumatics are highly associated to suicidal attempts, where in USA, the rates of exposures for OTC medications are in increase along with the increase in the use of these medications for suicidal attempts.[33] There are several additional factors that may contribute to this trend. These include alterations in prescribing practices, insufficient knowledge or education among parents and caregivers regarding the potential hazards linked to these medications, such as overdose or improper use. Psychosocial elements, such as mental health conditions, may also play a role. In the last two decades, there has potentially been a surge in the use of these medications among paediatric patients. This may be attributed to an escalation in the occurrence of ailments necessitating the administration of these medications or modifications in clinical protocols advocating for their use. Paediatric individuals sometimes exhibit complex medication regimens, particularly when they present with several diseases. The administration of many drugs to a single patient can elevate the likelihood of medication errors. Furthermore, enhanced awareness and reporting mechanisms have the potential to result in a higher documentation rate of occurrences, hence potentially contributing to the observed rise in hospital admissions associated with prescription errors.

The most common cause of hospital admissions was MAEs related to 4-aminophenol derivatives and other NSAID (propionic acid derivatives), which accounted for 79.3% and 16.0%, respectively. The 4-aminophenol derivatives are known to be used as analgesics and painkillers.[34] Their mechanism of action is to inhibit the synthesis of a selective prostaglandin,[35] and the most popular known derivative is acetaminophen (paracetamol).[36] The toxicity resulted from poisoning by acetaminophen a 4-aminophenol derivative and non-opioid analgesic is one of the most common causes of hepatic failure and 39% of patients required hospital admission to a tertiary care hospital.[37] Furthermore, 4-aminophenol derivatives toxicity are also associated with renal proximal tubules failure.[38] Our study found that MAEs related to the use of 4-aminophenol derivatives increased by 28.9% during the study period. This increase raised up despite the efforts made by the regulations to reduce the unintentional poisoning by acetaminophen by recommending special warning and OTC package labelling.[39] This increase included MAEs related to 4-aminophenol derivatives accidentally (unintentional), intentional self-harm or assault. Meanwhile, intentional poisoning by acetaminophen increased for 77.0% between the period 2004 and 2017 in Australia, as well as hospital admissions related to poisoning of acetaminophen increased annually by 3.3% in the same period.[38]

In our study, the age group below 15 years accounted for 8.9% of the total number of hospital admissions. MAEs related to non-opioid analgesics, antipyretics and antirheumatics is one of the most leading causes of poisoning in young children.[40] Previous studies suggest that elders are more likely to develop acetaminophen induced hepatotoxicity than younger ones. This is mainly due to the availability of the usage of enzyme inducing agents that

Table 2 Percentage change in the hospital admission rates

Hospitalisation cause	Rate of diseases in 1999 per 100 000 persons (95% CI)	Rate of diseases in 2020 per 100 000 persons (95% CI)	Percentage change from 1999 to 2020
Salicylates	2.78 (2.45 to 3.10)	0.89 (0.71 to 1.07)	−67.8
4-aminophenol derivatives	34.15 (33.00 to 35.30)	44.01 (42.76 to 45.27)	28.9
Pyrazolone derivatives	0.12 (0.05 to 0.19)	0.02 (−0.01 to 0.04)	−84.6
Non-steroidal anti-inflammatory drugs (propionic acid derivatives)	7.05 (6.53 to 7.58)	6.67 (6.19 to 7.16)	−5.4
Antirheumatics	0.05 (0.01 to 0.09)	0.01 (−0.01 to 0.03)	0.0
Non-opioid analgesics and antipyretics	1.32 (1.10 to 1.55)	0.19 (0.10 to 0.27)	−85.9
Non-pioid analgesic, antipyretic and antirheumatic, unspecified	0.69 (0.52 to 0.85)	0.00 (0.00 to 0.00)	−100.0

are more likely and most common in elders more than younger ones, and this is applicable for the incidence and the higher risk of gastrointestinal (GI) toxicity and renal failure associated with NSAIDs poisoning as well.[41]

Unfortunately, there is no gender stratification for the paediatric population in the medical databases used in this study. However, taking a wider look at the admissions related to MAEs for all age groups (unpublished data), we found that females contributed to 64.2% of the total number of hospital admissions. Females found to be more engaged in both deliberate self-harm and intentional self-harm behaviours.[42] This could be due to multiple factors including social and economic factors that contributed to an increased self-poisoning among females.[43] Body composition may affect the metabolism for acetaminophen by the increase of sulfate and the reduced amount of glucuronide, which makes these differences susceptible to toxicity.[44] Also other factors play a major role in the increased toxicity and increase the difference in the toxicity between males and females including the exposure to polypharmacy, self-harm attempts, dosing errors and non-adherence to medications.[45]

To the best of our knowledge, this is the first study to examine paediatric hospitalisation related to MAEs of non-opioid analgesics, antipyretics and antirheumatics in England and Wales. The utilisation of ecological study design holds significance in the identification of research questions that necessitate additional investigation

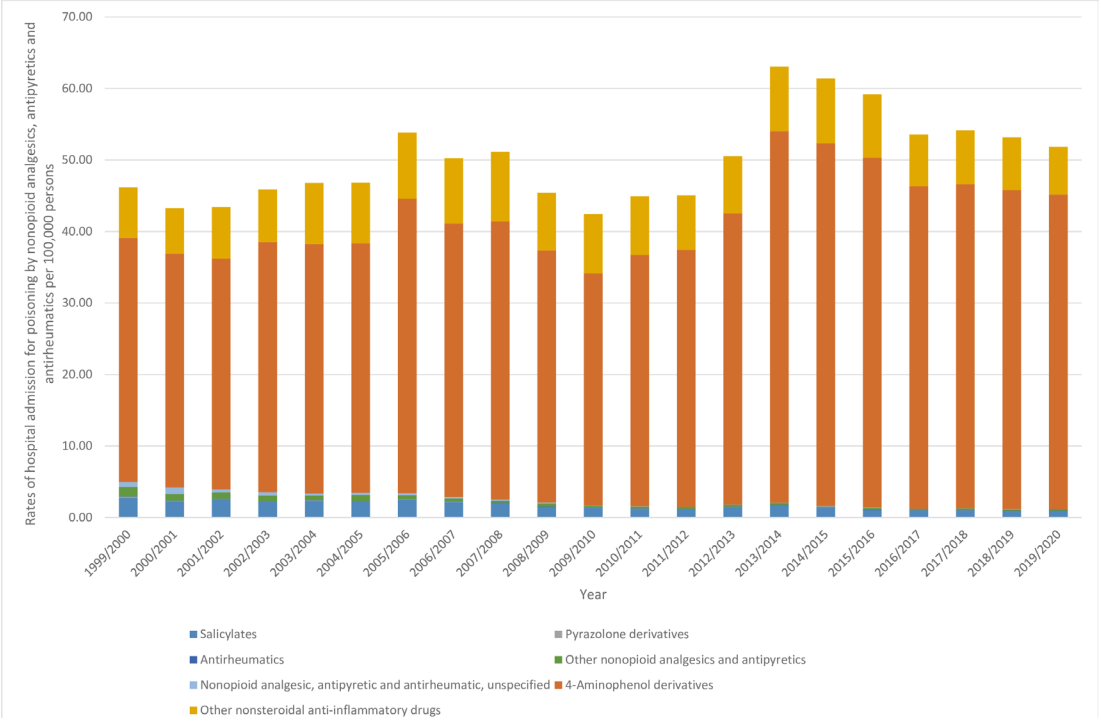

Figure 1 Rates of hospital admission between 1999 and 2020.

concerning hospitalisation patterns within the paediatric population. This study has limitations. The utilisation of population-level aggregated data posed limitations on our capacity to carry out patient follow-ups and discern noteworthy confounding variables. This may have resulted in an underestimation or overestimation of our hospitalisation rate. The utilisation of aggregated data has imposed limitations on the ability to obtain crucial patient demographic information, such as comorbidities and ethnicity. It is crucial to recognise that the absence of individual-level data hinders the ability to accurately determine the magnitude of variation. Hence, it is plausible that the confidence intervals derived from the aforementioned calculation may demonstrate imprecise results. Therefore, our findings should be interpreted carefully.

CONCLUSION

The study found a significant increase in the total annual number of hospital admissions related to poisoning by these drugs among the paediatric population. The most common reasons for MAEs were 4-aminophenol derivatives and other NSAIDs. The study suggests that the increase in hospital admissions is likely due to the increase in the use of OTC medications, which leads to an increase in the availability of these medications and the risk of deliberate or accidental overdose. The study highlights the need for further research to reduce the risk of poisoning by these drugs, especially among vulnerable populations, such as young children.

Correction notice This article has been corrected since it was first published. The author's name is 'Hassan Al-Shehri', and its affiliation has been updated.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study was approved by the Institutional Review Board at Isra University, Amman, Jordan gave their clearance with IRB No. SREC/22/08/84. This study was conducted in accordance with the World Medical Association (WMA) Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. Publicly available datasets were analysed in this study. Thes data can be found here: http://http//content.digital.nhs.uk/hes

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