Hospital admissions due to drug-related hyponatraemia

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Abstract

Little is known about morbidity due to drug-related hyponatraemia, despite hyponatraemia being a common side effect of frequently prescribed medicines. We conducted a 12-month retrospective service evaluation of hospital admissions due to drug-related hyponatraemia to determine what drugs are contributing factors, describe patient demographics and burden of morbidity. This was undertaken at a large acute UK hospital and drug-related hyponatraemia was defined by admissions where hyponatraemia was coded as the principal diagnosis and specific medication(s) were recorded as either contributory factor(s) or the principal cause of hyponatraemia and these medication(s) were discontinued. Of 131 hyponatraemia admissions, 71 (54%) were drug-related. Angiotensin converting enzyme inhibitors/ angiotensin receptor blockers, proton pump inhibitors and thiazide diuretics were drug classes most commonly associated. 61% of patients were women, median age 81 (IQR15.5) years, 61% were on more than 2 implicated drugs. The median length of stay was 4 (2-9 days IQR). This study highlights that elderly woman on more than 2 drugs that can cause hyponatraemia, constituted the majority of patients admitted to hospital with drug-related hyponatraemia.

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What is already known about this subject?

- Hyponatraemia (defined as serum sodium level <135mmol/L) is the most common electrolyte disturbance observed in clinical practice, with an estimated prevalence between 4.4% to 7.7% and is associated with increased mortality.
- Hyponatraemia is a side effect of different drug classes that are amongst the most commonly prescribed medicines in the UK and worldwide.
- There is a paucity of data on morbidity associated with drug-related hyponatraemia.

What does this study add?

- In this single centre study, the majority of patients admitted to hospital with drug-related hyponatraemia were elderly women on 2 or more drugs that can cause hyponatraemia.
- The median (interquartile range) duration of hospital admission due to drug-related hyponatraemia was 4 (2-9 days interquartile range) days.
- Angiotensin converting enzyme inhibitors/ angiotensin 2 receptor blockers and proton pump inhibitors were the most common medications identified as contributing to drug-related hyponatraemia hospitalisations.

Abstract:

Little is known about morbidity due to drug-related hyponatraemia, despite hyponatraemia being a common side effect of frequently prescribed medicines. We conducted a 12-month retrospective service evaluation of hospital admissions due to drug-related hyponatraemia to determine what drugs are contributing factors, describe patient demographics and burden of morbidity. This was undertaken at a large acute UK hospital and drug-related hyponatraemia was defined by admissions where hyponatraemia was coded as the principal diagnosis and specific medication(s) were recorded as either contributory factor(s) or the principal cause of hyponatraemia and these medication(s) were discontinued. Of 131 hyponatraemia admissions, 71 (54%) were drug-related. Angiotensin converting enzyme inhibitors/ angiotensin receptor blockers, proton pump inhibitors and thiazide diuretics were drug classes most commonly associated. 61% of patients were women, median age 81 (IQR15.5) years, 61% were on [?]2 implicated drugs. The median length of stay was 4 (2-9 days IQR). This study highlights that elderly woman on [?] 2 drugs that can cause hyponatraemia, constituted the majority of patients admitted to hospital with drug-related hyponatraemia.

Introduction:

Hyponatraemia (defined as serum sodium level <135mmol/L) is the most common electrolyte disturbance in clinical practice with an estimated prevalence between 4.4% to 7.7%. (1) A number of different drug classes can cause hyponatraemia. These include diuretics, angiotensin converting enzyme inhibitors (ACE-i)/ angiotensin receptor blockers (ARB), proton-pump inhibitors (PPI), non-steroidal inflammatory agents (NSAIDs) and anti-psychotic medications, all of which are amongst the most commonly prescribed medicines in clinical practice in the UK and worldwide. (2,3)

Prior studies have examined the association between individual classes of drug and hyponatraemia. A study of 114 geriatric inpatients observed that 3.4% of the patients on diuretics were hyponatraemic. (4) Advanced age and female gender have been observed as risk factors of thiazide-induced hyponatraemia. (5) A large population based study involving 32218 adults showed that in those over the age of 70, there is approximately three times higher risk of developing thiazide-induced hyponatraemia. (6)

Most of these studies evaluated hyponatraemia related to a specific class of drug (i.e diuretics and/or thiazide diuretics specifically). There is however, a paucity of data relating to morbidity associated with drug-related hyponatraemia or what classes of drugs are implicated in such morbidity. Therefore, we aimed to: 1) identify drugs associated as causal or contributing factor(s) in hospitalization principally due to drug-hyponatraemia 2) describe demographics of patients affected 3) quantify the burden of morbidity associated with drug-related hyponatraemia defined by hospitalization, by length of hospital stay and requirement of higher-level care 4) consider if any factors could mitigate morbidity (defined by hospitalization) due to drug-related hyponatraemia.

Methods:

This was a retrospective clinical service evaluation of 12 months hospital adult admissions (August 2019-2020) at Cambridge University Hospital, United Kingdom (UK). Admissions where hyponatraemia was coded as the principal diagnosis were reviewed and the validity of this diagnosis was checked from medical records. Drug-related hyponatraemia was defined by specific medication(s) recorded in the medical records as either a contributory or principal factor(s) in hyponatraemia presentation and discontinuation of these medication(s). Severity of hyponatraemia was defined by presence of symptoms and/or laboratory values (mild: 130-135 mmol/L, moderate: 125-129 mmol/L, severe <125 mmol/L). The project was approved by the hospital's audit and quality improvement board and as an evaluation of clinical service, did not require research ethics approval. Using electronic health care records, anonymised data from hospital admissions and primary care (available data from within hospital electronic healthcare records system) were extracted for in-depth review and analysis. Data where summarised are shown as average±(SD) or median (interquartile range) values.

Results:

Of 131 hospital admissions due to hyponatraemia, 71 (54%) were drug-related. Of these, drugs were a contributory factor or principal cause in 63% and 37% of cases respectively. Hospital length of stay was 4 (2-9 days IQR). Four (6%) patients required level 2 care or above. Forty-three (61%) of patients were women, with a median age of 81 (IQR 15.5) years. The demographics of patients are shown in Table 1. Admission sodium was 121±4.8 mmol/L and 56 out of 71 (79%) patients had severe hyponatraemia (<125 mmol/L). The majority (43/71, 61%) of patients were on [?]2 drugs associated with hyponatraemia and 10/71 (14%) were on [?]3 drugs. ACE inhibitors/ARB, proton pump inhibitors (PPI) and thiazide diuretics were the most common medications contributing to drug-related hyponatraemia, at 28%, 23% and 13% respectively, Figure 1.

Fifty-seven (80%) of patients had a laboratory serum sodium check within 6 months prior to admission, with a mean value of 132+-3.89mmol/L and 80% of patients had a repeat sodium check within 6-12 months post-discharge with a mean value of 133+-5.1 mmol/L. Twenty-six (37%) of the patients did restart their medication(s) determined as contributing factors within 12 months of their admission. Four (5%) were readmitted as inpatients within 12 months, but not due to hyponatraemia. It was not possible to evaluate the data to determine if medications re-started within the 12 months, were at lower doses.

Discussion:

This UK acute hospital evaluation of adult admissions due to hyponatraemia over a 12-month period, showed that elderly women on two or more drugs that can cause hyponatraemia make up the majority of hospitalisations due to drug-related hyponatraemia. This is therefore a high-risk group of patients for adverse drug reactions and their associated morbidity. Awareness of the potential cumulative effect of implicated drugs associated with hyponatraemia morbidity defined by hospitalisation, should be considered when prescribing these medications, and monitoring of patients who may be more at risk. ACE-inhibitors, proton-pump inhibitors and thiazide diuretics were medications most commonly associated with drug-related hyponatraemia hospitalisations in this study and are amongst the most commonly prescribed medications in the UK. (3)

Morbidity related to hyponatraemia in this small cohort of patients is worth highlighting. With a median length of stay of 4 days, and 6% of patients admitted to level 2 care, these data show that drug-related hyponatraemia is not an insignificant issue in terms of healthcare usage. The median length of stay for all medical admissions at our hospital within this period was 3 days (IQR 1-9 days). Moreover, this is likely not representative of the full scale of healthcare usage due to drug-related hyponatraemia, since these data are restricted to hospital admissions, where hyponatraemia was coded as the principal diagnosis only (and verified), and does not include patients who developed hyponatraemia during hospitalisation or those managed with drug-related hyponatraemia via ambulatory care or primary care pathways.

Pre and post hospital admission laboratory serum sodiums were evaluated in this study. Our data shows

that these were tested routinely; (80% within 6-months prior and 80% within 6-12 months post admission). These data show a mild hyponatraemia (132 mmol/L) in our cohort, and as such, it could be inferred that the admission with drug-related hyponatraemia that was evaluated, could not easily have been averted. It is likely an additional 'hit' such as intercurrent illness exacerbated this established mild hyponatraemia which led to a precipitous and serious drop in sodium and associated symptoms, necessitating hospital admission. This is consistent with our finding that drugs were identified as a contributing factor in 63% of cases, vs 37% of cases where they were identified as the principal factor in the hyponatraemia admission. Interestingly, although about 40% of patients were restarted on their medications within 12 months (highlighting the necessity of these medications and balance of benefit vs harm, they were not readmitted due to hyponatraemia), but 5% were re-admitted during this timeframe due to other causes.

ACE-inhibitors/ARBs, proton-pump inhibitors and thiazide diuretics were the drug classes most commonly identified as contributory medications in drug-related hyponatraemia hospitalisations. ACE-inhibitors were the largest (28%) contributing class overall, perhaps due to their indication as first line treatment for hypertension, heart failure and diabetic nephropathy. Hyponatraemia is listed as a rare side effect of ACE-inhibitor with an incidence of less than 1 in a 1000 (13) according to SmPC data. An accurate reflection of the real-world incidence of ACEi/ARB related hyponatraemia may be challenging to ascertain because they are so commonly prescribed and particularly when ACE-inhibitors are prescribed alongside other medications which affect water-sodium homeostasis. Deray *et al* found that 10 out of 17 case reports of ACE-inhibitor induced severe hyponatraemia were due to a combination with diuretics. (7) This is consistent with our findings, where more than half of patients who received ACE-I, were also on diuretics (12 out of 20 cases).

Hyponatraemia is also listed as a rare (<1/1000) adverse reaction of proton-pump inhibitors (14). However, given that PPIs are the most commonly prescribed medication in the UK, the number of possible cases may not be insignificant. A large population study observed that newly initiated proton-pump inhibitor therapy (within 90 days) increased the risk of hyponatraemia (adjusted odds ratio 2.78) leading to hospital admission. Female gender and the elderly were characteristics of those who required hospital admission due to hyponatraemia; which is in keeping with our study findings. (8) Buon*et al* showed that chronic use of proton-pump inhibitor also increased the risk of hyponatraemia in the elderly population. (9)

Thiazide diuretics were the third most common medication class identified in our study of drug-related hyponatraemia and identified in 13% of cases. Thiazides are one of the first line treatments for hypertension and a multi-centre retrospective cohort study showed a relative risk of 60% in developing hyponatraemia in patients treated with thiazides compared with ACE-I/ARB, beta-blocker or calcium channel blockers. The authors showed that the risk of developing thiazide-induced hyponatraemia persisted even up to 10 years of treatment suggesting that there may be insufficient follow-up after treatment initiation. (10)

We observed that the majority of patients in our study were elderly, female and on multiple medications that can cause hyponatraemia. These data are consistent with previous studies and highlights the characteristics of patients at risk of drug-related hyponatraemia and adverse drug reactions overall. (11,12)

Several mechanisms are postulated to explain this observation. Females may be more sensitive to the effect of hyponatraemia; and may have a different thirst response compared with males. The prescription rate for particular drug classes (which may cause hyponatraemia) may be higher in women. (5) 61% of patients in our study were on two or more medications associated with hyponatraemia, 14% on three or more. Polypharmacy is therefore likely an important factor in increasing the risk of hyponatraemia and particularly its associated morbidity, which disproportionately affects the elderly. A patient-centred approach to determine if medications can be optimized to reduce risk of hyponatraemia without compromising therapeutic effectiveness is important. This is based in the framework of systematic evaluation of polypharmacy and whether benefit/risk ratio is in favour to continue medications that can cause hyponatraemia in certain patients. Given that 40% of patients re-commenced their medications within 12 months, this suggests that in half of the patients this may have been the case.

Our study does have limitations. Firstly, the population is hospital admissions at a UK acute hospital,

where hyponatraemia was coded as principal admission diagnosis. Therefore, representation of morbidity due to drug-related hyponatraemia and our findings may not be applicable to a wider population or different healthcare systems. Secondly, although our cohort was selected for a coded primary diagnosis of hyponatraemia, drugs identifed as possible cause or contributory factor in the hyponatraemia presentation were based on explicit documentation by the medical team in the healthcare records of this and discontinuation of these medications during admission. Attribution of direct causality and burden of harm due to adverse drug reactions such as drug-related hyponatraemia from review of medical records and in delivery of clinical practice is challenging. However, in this small sized patient cohort , in-depth evaluation of each patient's hospital admission records was undertaken.This cohort included only patients admitted with hyponatraemia as a principal diagnosis and did not include patients who developed hyponatraemia during hospital admission or had hyponatraemia as an ancillary diagnoses.

In summary, this study highlights that elderly woman on multiple commonly prescribed medications that can cause hyponatraemia are most affected by morbidity from drug-related hyponatraemia. Morbidity evaluated in this study by hospitalization is not insignificant. Awareness of the characteristics of patients affected by drug-related hyponatraemia and an evaluation of this morbidity is important. Future work at a larger scale would be helpful to provide evidence that may support more frequent sodium monitoring in certain patient groups and integrated care pathways that may help reduce morbidity of hospitalization or length of stay associated with drug-related hyponatraemia.

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