signal

Tramadol and Hyponatraemia – new aspects of an old signal

Sara Hult, Uppsala Monitoring Centre

Summary

Tramadol is an opioid analgesic for treatment of moderate to severe pain. Hyponatraemia is an electrolyte disturbance especially common among elderly and hospitalised patients. In 2016, the Pharmacovigilance Risk Assessment Committee (PRAC) at the European Medicines Agency reviewed a signal of hyponatraemia and the syndrome of inappropriate anti-diuretic hormone secretion (SIADH) with tramadol, but causality was not established. The aim of our review was to investigate if VigiBase, the WHO global database of individual case safety reports, included cases suggestive of causality. VigiBase data up to 4 February 2018 for the broad MedDRA SMQ 'Hyponatraemia/SIADH' included 278 unique cases. A subset of 118 cases was reviewed case by case. In these 118 patients, the ages ranged between 20 and 106 years (median 77), with 35 patients younger than 65. Time-to-onset distribution was: within one day (21 cases), 2-7 days (56), 8-14 days (15), 15 days to 1 month (8) and >1 month (6). Seventy-nine patients recovered after tramadol withdrawal and one well-described positive rechallenge was identified. Tramadol was the sole suspect in 63 cases, and in 26 it was the sole reported drug. Potentially confounding conditions were described in a quarter of the cases. In another quarter, older diagnosed conditions were mentioned which were more likely to be risk factors than confounders. Fifty-five patients were co-treated with drugs known to cause hyponatraemia. In 19 cases these were reported as long-term drugs which had been taken for many months or years, and the reaction occurred only after tramadol was added. In five cases, tramadol was reported as being suspected of having interacted with the co-medications. VigiBase cases that support causality between tramadol and hyponatraemia were found. The key cases usually concerned elderly and predisposed patients, but young individuals were also identified. Causality was supported by the time-to-onset pattern and by cases with positive de- and re-challenge. The results were also strengthened by hypothesised mechanisms of actions, and findings in the literature.

Introduction

Tramadol is an opioid analgesic for treatment of moderate to severe pain. It is a non-selective pure agonist at μ-, δ- and κ-opioid receptors with a higher affinity for the μ-receptor. Other mechanisms for its analgesic effect involve inhibition of serotonin- and noradrenaline reuptake.[1] To exert full analgesic effect tramadol must be converted by CYP2D6 to its main metabolite O-desmethyltramadol (M1) which has a several-fold higher affinity for μ-opioid receptors than the parent drug. Tramadol is also converted by CYP3A4 and CYP2B6 to an inactive metabolite.[2] The inhibition of CYP3A4 and CYP2D6 may affect the plasma concentration of tramadol or M1.[3] Tramadol and its metabolites are almost completely excreted via the kidneys. An elimination half-life of up to three times longer than normal has been observed in patients with renal insufficiency.[4]

Hyponatraemia (HN) is characterised by serum sodium <135 mmol/L and is considered severe at <125 mmol/L. It is especially common among elderly and hospitalised patients with comorbidities and who are taking many drugs. Symptoms may include nausea, headache, decreased level of consciousness, seizures, impaired mental status, brain oedema and coma.[5] Chronic HN develops over a longer time (>48 hours) and is often asymptomatic. Acute HN has an onset of symptoms within 48 hours, with a higher risk of neurologic symptoms and death.[6] HN is usually classified according to volume status, i.e. hypovolemic HN (caused by vomiting, diarrhoea, renal losses and diuretics, especially thiazides), euvolemic HN (caused by hypothyroidism, stress, surgery, pain, the syndrome of inappropriate anti-diuretic hormone secretion (SIADH), and various drugs such as antiepileptics, antipsychotics, antidepressants, proton pump inhibitors (PPIs), ACE-inhibitors, angiotensin II antagonists and diuretics), or hypervolemic HN (caused by cirrhosis, heart failure, nephrotic syndrome and excessive fluid intake).[7] Drug-induced HN commonly emerges within the first few weeks of treatment.[8]

In 2016, the Pharmacovigilance Risk Assessment Committee (PRAC), at the European Medicines Agency, undertook a signal review of the association of '*Tramadol – Hyponatraemia and SIADH*'. The PRAC concluded that the data did not suggest a causal association since the number of cases was very low in view of the extensive post-authorisation exposure, and that many cases occurred in elderly patients and were confounded by concomitant therapy or other factors.[9] These arguments were not entirely convincing; tramadol-induced HN could be a very rare adverse drug reaction (ADR), which might explain the relatively low number of cases. HN may have many causes, and the diagnosis of drug-induced HN can easily be overlooked.[8] Lastly, as HN is largely predominant in the elderly population and is a symptom of various spontaneous or drug-induced conditions, it is inevitable that the reports mainly concern these patients. Considering all this, UMC decided to make its own review, to see if VigiBase, the WHO global database of individual case safety reports, included cases suggestive of causality between tramadol and HN.

Reports in VigiBase

As of 4 February 2018, there were 340 reports for tramadol and the broad MedDRA SMQ 'Hyponatraemia/SIADH'. Sixty-two duplicates were identified, leaving the number of unique cases as 278. The reports came from 24 countries, and the top five reporting countries were France (100 reports), United States (92), Australia (42), United Kingdom (21) and India (14). The IC/IC_{025} values were -0.1/-0.3 for HN and 1.1/0.7 for SIADH (September 2019).

To identify key cases our analysis focused on those with a time-to-onset available for tramadol, or where tramadol was the only reported drug in the structured data. For additional reports, with a potential of being key cases (e.g. where there was a start date for tramadol but no onset of reaction date), the narrative texts were further reviewed for time-to-onset information. Original reports were requested from national centres when possible and where thought to be of additional value. Cases with potentially confounding drugs (i.e. drugs with HN and/or SIADH listed as ADRs in their Summary of Products Characteristics (SmPCs)[10], and other opioids) reported as started within two months before or after tramadol start, were excluded. The remaining 118 cases were reviewed case by case. Twenty-eight were considered to be key cases. A selection of those are set out in the text or in Tables 3 and 4.

Case by case review of 118 cases

Age was available in 111 cases and ranged from 20 to 106 years old, with a median value of 77 years. The

age group distribution was 18-44 years (18 cases), 45-64 years (17), 65-74 years (14) and 75 years or older (62). Patient sex was 83 females and 34 males and was not reported for one.

Sixty-three cases were reported as serious, 11 reported convulsions and five were fatal. In four of the fatal cases the reported SMQ term was 'brain oedema' and HN was not mentioned. Two of these were overdoses and two were strongly confounded by existing condition. Only one fatal case clearly implicated HN:

> *A 27-year-old woman suffered a pelvic fracture after a motor vehicle accident. No other injuries were identified, and her serum sodium was normal. Pain relief was achieved with the maximum daily doses of paracetamol and tramadol. From the 5th day she showed symptoms of HN, and became a lot worse over the next days. Severe HN was detected (97 mmol/L) on the 9th day and she was transferred to intensive care. The corrective treatments of HN led to the development of osmotic demyelination syndrome, and the patient died.*

Potentially confounding conditions, including those that had recently appeared and were of an acute nature, e.g. major surgery, head trauma and recently worsened renal insufficiency, were given in approximately a quarter of the cases. Another quarter described conditions that the patients had had in the past or for a long time, such as chronic obstructive pulmonary disease (COPD), diabetes and hypothyroidism, which were more likely to be risk factors than confounders. One example is the case below (also a conference abstract by Farouk and Uribarri).

> *A 44-year-old male with a past medical history of hypothyroidism started with tramadol for leg pain. Within two weeks he presented to the emergency department with nausea and leg pain. He was euvolemic and had severe HN (109 mmol/L) and SIADH. Thyroid secreting hormone was within normal limits. The patient had no obvious source of SIADH other than tramadol. Tramadol was discontinued and fluid was restricted. By day 3, the patient was improving.*

The reference sodium values prior to taking tramadol were provided for nine patients among the key cases. In seven of these, the sodium levels were within the normal range but close to the lower limit for HN, while in one case the patient already had a slightly low sodium value when tramadol was initiated (the rechallenge case below).

The time-to-onset for tramadol was reported in 106 cases, see **Table 1**.

Table 1. Time-to-onset for tramadol and hyponatraemia

Time-to-onset	No. cases
0-1 day	21
2 to 7 days	56
8 to 14 days	15
15 days to 1 month	8
>1 month to 2 months	4
>2 months	2

Tramadol was withdrawn in 89 cases. The patient recovered after drug withdrawal in 79 cases, but 39 of these were also treated by either fluid restriction, saline infusion or sodium orally, and in 11 cases there was at least one other drug withdrawn. In 34 cases positive dechallenge was reported for tramadol without mentioning any other corrections or dechallenge of other drugs.

There was one well-described case with a positive rechallenge (also a publication by Udy et al).

> *A 79-year-old female was treated with tramadol for post-operative pain after knee replacement surgery on two occasions with a six months gap in between. Her regular medication included indapamide and valsartan, both known to cause HN. Fentanyl (another opiate) was administered pre-operative. Her pre-operative serum sodium was 131 mmol/L. The day after surgery her sodium levels dropped rapidly to 115 mmol/L. Tramadol was stopped and HN was corrected with fluid restriction. The same happened after the second operation. The major confounding drug, indapamide, was only taken at the time of the first operation and had been discontinued at the time of the second. Surgery itself is a confounder. The case was very complex and the cause of HN was probably multifactorial.*

Another three cases also gave indications of positive

rechallenge but the reports were not very informative. They described patients who had developed HN during tramadol treatment in the past, and that tramadol was the suspected cause.

> *A 47-year-old female presented three times with SIADH and severe HN, and each time she was treated with tramadol. Her sodium level was normalised after tramadol was stopped.*

Tramadol was the sole suspected drug in 63 of the selected cases and was the only reported drug in 26 of these. A majority of the 63 cases were sparsely documented or confounded by other conditions.

Fifty-five cases had co-suspected or concomitant drugs with HN and/or SIADH listed as ADRs in their UK SmPCs, see **Table 2**.

Table 2. Co-suspected or concomitant drugs with HN and/or SIADH listed as ADRs in UK SmPCs

Drug groups	No. cases
Thiazide and thiazide-like diuretics	19
Proton pump inhibitors	18
Angiotensin II antagonists	16
ACE-inhibitors	15
Antidepressants	10
Loop diuretics	7
Spironolactone	6
Antiepileptics	5
Antipsychotics	3
Benzodiazepines	3
Antiarrhythmics	2
Osmotically acting laxatives	2

In 19 of the 55 cases these were clear long-term drugs, and HN occurred only after tramadol initiation;

> *In 10 there were full dates, showing that treatment with the HN risk drugs had been ongoing for a period of between 2.5 months and 19 years before tramadol was started. Six of these were among the key cases and are further described in Table 3. Two were sparsely documented and two were confounded.*
>
> *In nine cases there were no exact dates for the HN risk drugs, but they were described as long-term treatment. Four of these are listed in Table 4. In one case, all drugs except tramadol (including valpromide) had been taken for several years (case 8). In two cases, the patients were taking selective serotonin reuptake inhibitors (SSRIs) as long-term treatment when tramadol was started for back pain (cases 10, 12). In another example (case 11), the patient was taking a thiazide diuretic, an angiotensin II antagonist and a PPI long term when tramadol was initiated.*

In five cases, tramadol was reported as suspected of having interacted with the co-medications. One example is described below:

> *A 56-year-old female received tramadol drops for chronic back pain. The patient was also treated with venlafaxine, zolpidem, lorazepam and quetiapine, whose doses had not recently been modified. Tramadol abuse was suspected but the dose unknown. She was hospitalised the next day with acute HN, renal failure, rhabdomyolysis, inflammation and respiratory acidosis. The symptoms were suspected to be a result of serotonin syndrome or neuroleptic syndrome, from an interaction or an overdose. Tramadol and venlafaxine (an SSRI) were reported as interacting.*

Literature and Labelling

Abadie et al published a review describing all serious adverse drug reactions (SADRs) with tramadol notified to the French pharmacovigilance centres and pharmaceutical companies between 2010 and 2011,[11] and a similar study described all reported SADRs in the French national pharmacovigilance database between 2011 and 2015.[12] In both analyses, HN was highlighted as an unexpected SADR but causality assessments were not done. Buon et al suggested that co-treatment with PPIs and tramadol potentiates the risk of HN.[13] In a population-based study it was suggested that the use of tramadol, compared to use of codeine, was associated with an increased risk of HN requiring hospitalization.[14] But according to Chevalier et al codeine is not an appropriate comparator to tramadol, because of their differing therapeutic traditions.[15]

Seven published case reports from between 2004 and 2018 were found in the literature[16-22], of which

five were included in the dataset of 340 reports in VigiBase.[16-20] Two consisted of more than one case:[16,21] 1) In Hunter from 2004, a 76-year-old woman developed HN nine days after tramadol was added to regular treatment including perindopril, an ACE-inhibitor, and other concomitant drugs. HN did not resolve after fluid restriction but only after tramadol cessation.[16] The author also mentioned other elderly patients who had taken tramadol for pain control after fractures and developed HN, which was corrected on cessation of tramadol. One of these cases occurred when tramadol was given to a patient already on citalopram, an SSRI. He recommended that "*Sodium concentrations should be monitored when prescribing tramadol particularly in the elderly and those taking other medications, such as SSRIs and diuretics, which also predispose to HN.*" 2) In Yong and Khow from 2018, two similar cases are described, of women aged 70 and 86 who received tramadol for fracture pain. They both had perindopril, an ACE-inhibitor, in their regular medication, for which HN is a known ADR. The 86-year old was also taking omeprazole. Both had diabetes type 2. After one week and three days respectively, their sodium levels had dropped to 123 and 121 mmol/L. They were euvolemic and SIADH was indicated. Tramadol was stopped and replaced with oxycodone, and they had fluid restriction. Both recovered within a few days after cessation of tramadol.[21] Three additional case reports published in conference abstracts were found during the assessment of the VigiBase reports.[23-25] Five of the above case reports were published after the PRAC's 2016 review.[21-24]

Neither HN nor SIADH are acknowledged ADRs for tramadol in the EU and US.[1,8,26] Only one of 16 Marketing Authorisation Holders with SmPCs for tramadol in the UK Electronic Medicines Compendium has listed HN as an ADR (and then only for the drops formulation, and not in their tablet SmPCs).[4] In Canada, HN is described in tramadol's product monographs.[27] In Australia and New Zealand, both HN and SIADH are included in the product information.[28,29]

CYP2D6 and CYP3A4 inhibitors (such as some SSRIs, SNRIs, quetiapine and haloperidol) and CYP3A4 inducers (such as carbamazepine) may alter the plasma concentration of tramadol and its metabolites. Antidepressants (such as SSRIs and mirtazapine) in combination with tramadol increases the risk of serotonin syndrome and convulsions.[1,26] In the EU, US, Australian and New Zealand sources there is no information stating that interactions could lead to an increased risk of HN. The monographs from Health Canada state that the use of tramadol with drugs that can decrease electrolyte levels (including loop- and thiazide diuretics, laxatives and enemas, high-dose corticosteroids and PPIs) should be avoided as far as possible.[27]

It has been hypothesized that tramadol-induced HN may involve both its serotonin and opioid pathways, leading to anti-diuresis.[20] Opioids are involved in very complex regulatory mechanisms, including vasopressin and the renin-angiotensin-aldosterone system, and they also have diuretic properties.[30,31] A third pathway that may be involved is tramadol's inhibition of noradrenaline reuptake; noradrenaline also regulates vasopressin and has been attributed to both anti-diuretic and diuretic effects.[32-34]

Discussion

Cases in VigiBase that support causality between tramadol and HN were identified. The key cases usually concerned elderly and predisposed patients. There were also suggestive cases in the younger age groups, even though they were few in comparison.

The evidence for causality included consistent temporal relationships between tramadol initiation and the onset of reaction; in more than half of the cases with onset dates reported, the time-to-onset ranged between 2 to 7 days. In a notable proportion of the cases, HN developed with a time-to-onset less than 2 days. This is unusual for drug-induced HN and suggests that additional or other causes were involved. Many patients were clearly in an at-risk group and they may already have been close to the border of low sodium levels when tramadol was started.

There were 79 cases with a reported positive dechallenge, and one well documented case of a positive rechallenge. In 34 of these cases there were no other corrective treatments of HN (e.g. fluid restriction or dechallenge of other drugs) reported.

There are several possible mechanisms of actions for tramadol-induced HN, involving the opioid, serotonin and noradrenaline pathways. But these neurotransmitters are all active in very complex

regulatory mechanisms and their functions are sometimes contradictory; e.g. opioids and noradrenaline may have both diuretic and anti-diuretic properties. Therefore the exact mechanisms for tramadol-induced HN may be difficult to fully understand, and tramadol's ability to cause HN may be very unpredictable.

In many of the key cases and the published literature cases, HN developed only after tramadol was added to regular treatment of drugs with the potential of causing HN or SIADH. The most frequent drug groups were: PPIs, SSRIs and other antidepressants, diuretics, angiotensin II antagonists and ACE-inhibitors. The temporal pattern in these cases indicates that these co-reported drugs are risk-factors for tramadol-induced HN.

For some of these risk-drug groups there are possible pharmacokinetic mechanisms for drug-drug interactions with tramadol. Inhibitors of CYP2D6 and CYP3A4, and inducers of CYP3A4, may influence the metabolism of tramadol.[1,26] In the case with the 56-year-old woman, a drug interaction was suspected between the SNRI venlafaxine, a CYP2D6 inhibitor, and tramadol. The same patient was also treated with quetiapine, another inhibitor of both CYP2D6 and CYP3A4, which could also have affected the plasma levels of tramadol and its metabolites. Diuretics, angiotensin II antagonists and ACE-inhibitors have the potential to cause renal insufficiency, and renal insufficiency may prolong the elimination half-life of tramadol. But such drug-drug interactions are not described in the UK SmPC or the US product label for tramadol.[1,26]

Patients and healthcare professionals should be aware of the risk of tramadol-induced HN, particularly in cases concerning elderly and predisposed patients, and when there is co-treatment with other drugs known to cause HN. The risk may be highly unpredictable due to tramadol's complex mechanisms of actions.

Conclusions

VigiBase cases and published case reports that support causality between tramadol and HN were found. The key cases usually concerned elderly and predisposed patients, but young individuals were also identified. Causality was supported by the time-to-onset pattern, cases with positive dechallenge and one positive rechallenge. Co-treatment with drugs with the potential to cause HN seem to be risk-factors of tramadol-induced HN, and in some cases pharmacokinetic drug-drug interactions may have occurred. These findings are supported by hypothesised mechanisms of actions.

References

1. Electronic Medicines Compendium. SmPC for Zydol XL 150 mg prolonged-release tablets. Available from: https://www.medicines.org.uk/emc/product/85/smpc. Accessed: 18 June 2019.

2. Orliaguet G, Hamza J, Couloigner V, Denoyelle F, Loriot MA, Broly F, Garabedian EN. A case of respiratory depression in a child with ultrarapid CYP2D6 metabolism after tramadol. Pediatrics. 2015 Mar;135(3):e753-5.

3. Dean L. Tramadol therapy and CYP2D6 genotype. In: Pratt V, McLeod H, Rubinstein W, Dean L, Kattman B, Malheiro A, editors. Medical Genetics Summaries [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2012-. 2015 Sep 10.

4. Electronic Medicines Compendium. SmPC for Tramadol 100 mg/ml oral drops, solution. Available from: https://www.medicines.org.uk/emc/product/4648/smpc. Accessed: 18 June 2019.

5. Medscape. Available from: https://emedicine.medscape.com/article/242166-overview. Accessed: 16 June 2019.

6. Sahay M, Sahay R. Hyponatremia: A practical approach. Indian J Endocrinol Metab. 2014 Nov-Dec; 18(6):760-71.

7. MSD Manual. Available from: https://www.msdmanuals.com/professional/endocrine-and-metabolic-disorders/electrolyte-disorders/hyponatremia. Accessed: 16 June 2019.

8. Pharmacovigilance Risk Assessment Committee (PRAC). Minutes of the PRAC meeting 04-08 July 2016. Available from: https://www.ema.europa.eu/en/committees/prac/prac-agendas-minutes-highlights. Accessed: May 2019.

9. Liamis G, Milionis H, Elisaf M. A review of drug-induced hyponatremia. Am J Kidney Dis. 2008 Jul;52(1):144-53.

10. Electronic Medicines Compendium. Available from: http://www.medicines.org.uk/emc. Accessed: 16 June 2019.

11. Abadie D, Durrieu G, Roussin A, Montastruc JL; Réseau Français des Centres Régionaux de Pharmacovigilance. Effets indésirables « graves » du tramadol : bilan 2010-2011 de pharmacovigilance en France. Thérapie. 2013 Mar-Apr;68(2):77-84.

12. Moulis F, Rousseau V, Abadie D, Masmoudi K, Micallef J, Vigier C, Pierre S, Dautriche A, Montastruc F, Montastruc JL. [Serious adverse drug reactions with tramadol reported to the French pharmacovigilance database between 2011 and 2015]. Thérapie. 2017 Dec;72(6):615-24.

13. Buon M, Gaillard C, Martin J, Fedrizzi S, Mosquet B, Coquerel A, Peyro Saint Paul L. Risk of proton pump inhibitor-induced mild hyponatremia in older adults. J Am Geriatr Soc. 2013 Nov;61(11):2052-4.

14. Fournier JP, Yin H, Nessim SJ, Montastruc JL, Azoulay L. Tramadol for noncancer pain and the risk of hyponatremia. Am J Med. 2015 Apr;128(4):418-25.

15. Chevalier P, Smulders M, Chavoshi S, Sostek M, LoCasale R. A description of clinical characteristics and treatment patterns observed within prescribed opioid users in Germany and the UK. Pain Manag. 2014 Jul;4(4):267-76.

16. Hunter R. Tramadol and hypontraemia. Australian prescriber. 2004;27(5):97.

17. Udy A, Deacy N, Barnes D, Sigston P. Tramadol-induced hyponatraemia following unicompartmental knee replacement surgery. Anaesthesia. 2005 Aug;60(8):814-6.

18. Long S, Neale G, Vincent C. The competent novice: practising safely in the foundation years. BMJ. 2009 Apr 11;338(7699):887-90.

19. Le Berre JP, Desramé J, Lecoules S, Coutant G, Béchade D, Algayres JP. [Hyponatremia due to tramadol]. Rev Med Interne. 2007 Dec;28(12):888-9.

20. Lota AS, Dubrey SW, Wills P. Profound hyponatraemia following a tramadol overdose. QJM. 2012 Apr;105(4):397-8.

21. Yong TY, Khow KS. Hyponatraemia associated with tramadol use: A Case Report. Curr Drug Saf. 2018 May 8.

22. Garakani A. Hyponatremia associated with tramadol in a patient with alcohol use disorder and anxiety taking desvenlafaxine. Prim Care Companion CNS Disord. 2018 Dec 13;20(6).

23. Farouk SS, Uribarri J. After tramadol use (Abstract). 19th International Conference on dialysis, Advances in chronic kidney disease 2017, February 1-3, 2017, Las Vegas, NV: Abstracts. Blood purif. 2017;43(1-3):244-78 p. 269.

24. Rouxinol P, Pedro L, Faria D, Santos C, Arez L. Hiponatremia de causa iatrogénica. XXII Congresso nacional de medicina interna e V Congresso iberico de medicina interna. 2016. 491.

25. King R, Khan S, Rajaswaren C. A rare cause of a common problem. Endocrine Abstracts; July 2010: 1; p. 77.

26. Daily Med. Product label for tramadol (Ultram®). Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=45f59e6f-1794-40a4-8f8b-3a9415924468. Accessed: 18 June 2019.

27. Health Canada. Product monograph for tramadol (Auro-Tramadol®). Available from: https://health-products.canada.ca/dpd-bdpp/info.do?lang=en&code=97034. Accessed: 18 June 2019.

28. Therapeutic Goods Administration. Product information for tramadol (Tramal®). Available from: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/PICMI?OpenForm&t=&q=tramadol. Accessed: 18 June 2019.

29. Medsafe. Product information for tramadol (Tramal®). Available from: https://www.medsafe.govt.nz/profs/Datasheet/t/TramalcapSRtabinjoraldrops.pdf. Accessed: 18 June 2019.

30. Vuong C, Van Uum SH, O'Dell LE, Lutfy K, Friedman TC. The effects of opioids and opioid analogs on animal and human endocrine systems. Endocr Rev. 2010 Feb;31(1):98-132.

31. Fukuhara M, Matsumura K, Abe I, Fujishima M. Interaction of opioids and vasopressin in central action of angiotensin II in conscious rabbits. Hypertens Res. 1998 Jun;21(2):89-95.

32. Krothapalli RK, Suki WN. Functional characterization of the alpha adrenergic receptor modulating the hydroosmotic effect of vasopressin on the rabbit cortical collecting tubule. J Clin Invest. 1984 Mar;73(3):740-9.

33. Sevcik J, Nieber K, Driessen B, Illes P. Effects of the central analgesic tramadol and its main metabolite, O-desmethyltramadol, on rat locus coeruleus neurones. Br J Pharmacol. 1993 Sep;110(1):169-76.

34. Tsushima H, Mori M, Matsuda T. Antidiuretic effects of alpha- and beta-adrenoceptor agonists microinjected into the hypothalamic paraventricular nucleus in a water-loaded and ethanol-anesthetized rat. Jpn J Pharmacol. 1986 Feb;40(2):319-28.

Table 3. Key cases with clear start dates for the hyponatraemia risk drugs

Case	Age/ Sex	Medical history	Suspected (S), interacting (I) or concomitant (C) drugs Underline = HN risk drugs	Time to onset	Actions taken/ Outcome	Case summary
1	88/F	-	Indapamide, tramadol (S) Clopidogrel, felodipine, paracetamol, risedronic acid, dorzolamide/timolol, latanoprost (C)	5 days	Drug withdrawn/ Reaction abated	An 88-year-old female with indapamide for 3 years started tramadol for sciatic (ichias) pain. After 5 days she was diagnosed with very low sodium levels (104 mmol/L) and hypokalaemia. Her sodium reference value was 135-145 mmol/L. Treatment of reaction was cessation of therapy.
2	81/F	Breast cancer, COPD, hypertension	Hydrochlorothiazide/ valsartan, tramadol (S) Budesonide/ formoterol, ramipril, verapamil (C)	1 day	Drug withdrawn/ Unknown Oral potassium and sodium, and fluid replacement	An 81-year-old female was taking hydrochlorothiazide, valsartan and ramipril for 3 years. She took tramadol for pain after tooth extraction, after which she had repeated vomiting (4-5 times). The next day she was admitted to hospital for deterioration of general condition. HN and hypokalaemia were found and she was hospitalized for 3 days. Tramadol and hydrochlorothiazide were discontinued on the first day and vomiting stopped. Valsartan was continued.
3	73/F	Hypertension, back pain, thrombo-embolic accident	Calcitonin, tramadol, losartan, furosemide, paracetamol (S) Enoxaparin (C)	13 days	Drug withdrawn/ Reaction abated Sodium correction	A 73-year-old female had been taking furosemide and losartan for 3 years, paracetamol and enoxaparin for an unknown period, and calcitonin for a week when tramadol was introduced for back pain. After 13 days she had asthenia, nausea, vomiting, depressive state and increased back pain. Codeine, amitriptyline, tetrazepam and lactulose were added. Severe HN (114 mmol/L) and hypokalemia was found 2 days later, and she was very confused. At hospital all medications except enoxaparin were stopped, and sodium chloride was administered. A week later she was recovering and losartan reintroduced. Note: Amitriptyline may cause HN but was started after the first symptoms.
4	75/F	Hypertension, atrial fibrillation	Captopril/ hydrochlorothiazide, tramadol (S) Paracetamol (C)	12 days	Drug withdrawn/ Reaction abated	A 75-year-old female patient, who had been taking captopril, hydrochlorothiazide and paracetamol since the year before (>7 months), started tramadol treatment for unspecified pain. After 12 days SIADH was reported. Eight days later all drugs except paracetamol were stopped. The patient recovered.
5	88/F	Trigeminal neuralgia	Atenolol, carbamazepine, losartan, tramadol (I) Alprazolam (C)	11 days	Drug withdrawn/ Reaction abated	An 88-year-old female had been treated with carbamazepine for trigeminal neuralgia for 1.5 years, atenolol 1.5 years, and losartan 1 year when she started tramadol treatment. After 11 days HN was diagnosed. An interaction was reported between tramadol, carbamazepine, atenolol and losartan. The first three were discontinued, and the losartan dose was increased.

6	96/F	Hypertension arterial, thyroid cancer, thrombosis venous deep, osteoporosis	Indapamide/ perindopril, Tramadol (S) Levothyroxine, warfarin, calcium carbonate/ colecalciferol, risedronic acid, ginkgo biloba, zopiclone (C)	7 days	Drug withdrawn/ Reaction abated Fluid restriction	A 96-year-old female suffered from hip pain after a fall. She had been on indapamide and perindopril for 19 years and concomitant drugs for an unknown time. She was prescribed tramadol. A week later she was extremely tired and was vomiting. Her sodium level was 128 mmol/L and her TSH higher than normal (medicated for hypothyroidism since unknown). Two days later she was hospitalized, tramadol was stopped and fluid was restricted. The following week she recovered.

Table 4. A selection from the additional key cases

Case	Age/ Sex	Medical history	Suspected (S), interacting (I) or concomitant (C) drugs Underline = HN risk drugs	Time to onset	Actions taken/ Outcome	Case summary
7	84/F	Alzheimer's disease, ulcer gastroduodenal	Tramadol (S) Calcium, cetornan, vitamine D3, metoclopramide (C)	3 days	Drug withdrawn/ Reaction abated Fluid restriction	An 84-year-old female was hospitalised for back pain from a spine fracture. At admission her sodium level was normal at 136 mmol/L. She received tramadol for the pain. Three days later, severe HN at 121 was found. She improved after stopping tramadol and fluid restriction.
8	45/M	Diabetes type 2, psychosis	Fluphenazine, tramadol, valpromide (S) Acarbose, calcium carbonate, clonazepam, glucophage loxapine, trihexyphenidyl, pravastatin, risedronate (C)	4 days	Drug withdrawn/ Unknown	A 45-year-old male received tramadol for hip dislocation on two occasions. Four days after the first occasion, HN with a sodium level at 134 mmol/L (ref. 137 mmol/L) appeared, which further decreased to 130 over the next 6 days. Tramadol was stopped a week later, and her sodium level rose to 133. All drugs except tramadol had been taken for several years.
9	43/F	Psychosis manic-depressive, convulsions, chronic alcohol abuse	Escitalopram, haloperidol, olanzapine, tramadol (S) Nicotinamide, oxazepam, pyridoxine, thiamine, zopiclone (C)	2 days	Drug withdrawn/ Reaction abated Fluid restriction	A 43-year-old female was taking escitalopram for 2 months, olanzapine for more than a year, and haloperidol and oxazepam for an unknown period. She started tramadol for tooth pain. After 2 days she was hospitalised after a seizure with loss of consciousness and severe HN (120 mmol/L). HN was corrected with fluid restriction, tramadol and escitalopram were stopped and the patient recovered.
10	63/M	Epilepsy, hypertension arterial, mental retardation	Escitalopram, tramadol (S) Lamotrigine, manidipine (C)	A few days	Drug withdrawn/ Reaction abated	A 63-year-old male was taking escitalopram as a long-term treatment and tramadol for a few days for back pain. His medical history included epilepsy but the patient had been free from convulsion for a year. He was hospitalized for convulsions and severe HN (121 mmol/L), and lab values indicated SIADH. Escitalopram and tramadol were suspected drugs. The patient recovered after dechallenge of tramadol while escitalopram was switched to citalopram.

11	70/F	Cholecystectomy, hypertension arterial	Hydrochlorothiazide/ olmesartan, Paracetamol/ tramadol, Tramadol (S) Acetylsalicylic acid, manidipine, nadolol, pantoprazole, zolpidem (C)	7 days	Drug withdrawn/ Reaction abated	A 70-year-old female with hip pain was treated with paracetamol and tramadol. Seven days later she was hospitalised for decreased consciousness and convulsions. Severe HN at 118 mmol/L was found (normal levels two months earlier) with indication of SIADH. Hydrochlorothiazide, olmesartan and all concomitants were being taken long-term. Hydrochlorothiazide, olmesartan, paracetamol and tramadol were stopped and sodium normalised.
12	79/F	Depression, psychosis	Tramadol (S) Citalopram, olanzapine, valproic acid (C)	20 days	Drug withdrawn/ Reaction abated Fluid restriction	A 79-year-old female developed acute HN (121 mmol/L) after recent (20 days) tramadol treatment start. All other drugs were reported as "long-term". The indication for tramadol was back pain. The sodium level went back to normal after cessation of tramadol only and fluid restriction.
13	86/F	-	Tramadol (S) Alendronic acid, codeine, enalapril, mirtazapine, paracetamol (C)	2 days	Drug withdrawn/ Reaction abated	An 86-year-old female was hospitalised due to back pain. She had been taking ongoing medications since an unknown date. Her sodium was 137 mmol/L at admission. Tramadol was initiated. Two days later her sodium had fallen to 122 mmol/L, and again to 119 after another two days. Tramadol was suspected and treatment stopped on day 4. On day 5 the sodium increased again and was back to normal on day 7.
14	75/F	-	Candesartan/ hydrochlorothiazide, dextropropoxyphene/ paracetamol, tramadol (S) Celecoxib, esomeprazole, trihexyphenidyl (C)	8 days	Drug withdrawn/ Reaction abated Fluid restriction	A 75-year-old female took tramadol for back pain. After 8 days she had HN at 118 mmol/L (reference 140), which resulted in admission to hospital. SIADH was diagnosed. She had candesartan, hydrochlorothiazide taken "long-term" an esomeprazole since an unknown date. She recovered after fluid restriction and cessation of all three suspected drugs.
15	90/F	Hypothyroidism, cholecystitis, osteoporosis, fracture, recurring falls, dehydration, depression, cognitive problems, hypertension, acute pancreatitis	Mirtazapine, spironolactone, tramadol, tetrazepam (I) Alendronic acid, paracetamol, calcium, levothyroxine, pantoprazole (C)	3 days	Drug withdrawn/ Reaction abated	A 90-year-old female was being treated with mirtazapine and spironolactone since unknown. Her concomitants were long-term. She had a fall and contusion of chest wall with intense pain, and were treated with tramadol, paracetamol and tetrazepam. Three days later she was nauseous, confused and vomited. On the 4th day she was hospitalized and profound HN (112 mmol/L) was found. Her TSH levels were normal. No renal or hepatic insufficiency, ECG abnormalities or infections were found. Orthostatic hypotension investigation was negative. There was a positive dechallenge for tramadol, mirtazapine, spironolactone and tetrazepam. The sodium levels and confusion improved after 48 hours and she had recovered 10 days later (Na 137 mmol/L).

SIGNAL

WHO defines a signal as:

"Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously". An additional note states: "Usually more than one report is required to generate a signal, depending on the seriousness of the event and the quality of the information".*

A signal is therefore a hypothesis together with supporting data and arguments. A signal is not only uncertain but also preliminary in nature: the situation may change substantially over time one way or another as more information is gathered. A signal may also provide further documentation of a known association of a drug with an ADR, for example: information on the range of severity of the reaction; the outcome; postulating a mechanism; indicating an "at risk" group; a dose range which might be more suspect; or suggesting a pharmaceutical group effect or a lack of such an effect by a particular drug.

Signals communicated by UMC are derived from VigiBase, the WHO global database of individual case safety reports. This database contains summaries of individual case safety reports of suspected adverse drug reactions, submitted by national pharmacovigilance centres (NCs) that are members of the WHO Programme for International Drug Monitoring. More information regarding the status of this data, its limitations and proper use, is provided in the Caveat on the last page of this document.

VigiBase is periodically screened to identify drug-ADR combinations that are unknown or incompletely documented. Combinations of such interest that they should be further reviewed clinically are sent to members of the Signal Review Panel for in-depth assessment. The Signal Review Panel consists of experienced international scientists and clinicians, usually affiliated with a governmental or an academic institution. The expert investigates the clinical evidence for the reaction being related to the suspected drug.

The topics discussed in the signals represent varying levels of suspicion. Signals contains hypotheses, primarily intended as information for the national regulatory authorities. They may consider the need for possible action, such as further evaluation of source data, or conducting a study for testing a hypothesis.

The distribution of signals is currently restricted to NCs, regulatory authority staff and their advisers, participating in the WHO Programme. Signals are sent to the pharmaceutical companies when they can be identified as uniquely responsible for the drug concerned. UMC does not take responsibility for contacting all market authorisation holders. As a step towards increased transparency, since 2012 UMC signals are subsequently published in the WHO Pharmaceuticals Newsletter.

National regulatory authorities and NCs are responsible for deciding on action in their countries, including communicating the information to health professionals, and the responsible market authorisation holders, within their jurisdiction.

In order to further debate, we encourage all readers of signals to comment on individual topics.

* Edwards I.R, Biriell C. Harmonisation in pharmacovigilance. Drug Safety 1994;10:93-102.

Responses from industry

Signals on products under patent are submitted to patent holders for comments. Responses from industry are unedited. The calculations, analysis and conclusions are theirs, and should be given serious but critical consideration in the same way as any scientific document. The WHO and UMC are not responsible for their findings, but may occasionally comment on them.

Caveat Document

Statement of reservations, limitations and conditions relating to data released from VigiBase, the WHO global database of individual case safety reports (ICSRs). Understanding and accepting the content of this document are formal conditions for the use of VigiBase data.

Uppsala Monitoring Centre (UMC) in its role as the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO Programme for International Drug Monitoring. The information is stored in VigiBase, the WHO global database of individual case safety reports (ICSRs). It is important to understand the limitations and qualifications that apply to this information and its use.

Tentative and variable nature of the data

Uncertainty: The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product is the cause of an event, rather than, for example, underlying illness or other concomitant medication.

Variability of source: Reports submitted to national centres come from both regulated and voluntary sources. Practice varies: some national centres accept reports only from medical practitioners; others from a broader range of reporters, including patients, some include reports from pharmaceutical companies.

Contingent influences: The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the adverse effects and other factors.

No prevalence data: No information is provided on the number of patients exposed to the product, and only a small part of the reactions occurring are reported.

Time to VigiBase: Some national centres make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of an ICSR by a national centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from that obtained directly from national centres.

For these reasons, interpretations of adverse effect data, and particularly those based on comparisons between medicinal products, may be misleading. The data comes from a variety of sources and the likelihood of a causal relationship varies across reports. Any use of VigiBase data must take these significant variables into account.

Prohibited use of VigiBase Data includes, but is not limited to:

- patient identification or patient targeting
- identification, profiling or targeting of general practitioners or practice

Any publication, in whole or in part, of information obtained from VigiBase must include a statement:

(i) recording 'VigiBase, the WHO global database of individual case safety reports (ICSRs)' as the source of the information

(ii) explaining that the information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases

(iii) affirming that the information does not represent the opinion of the UMC or the World Health Organization.

Omission of this statement may exclude the responsible person or organization from receiving further information from VigiBase.

UMC may, in its sole discretion, provide further instructions to the user, responsible person and/or organization in addition to those specified in this statement and the user, responsible person and/or organization undertakes to comply with all such instructions.