Ibuprofen-associated hypokalemia and metabolic acidosis: systematic literature review

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Abstract

Objective: Ibuprofen is a widely used nonsteroidal anti-inflammatory drug, which has been occasionally associated with hypokalemia and metabolic acidosis. The objective of this report is to analyze the literature on this issue and to address the underlying pathophysiology. **Data Sources:** Excerpta Medica, the National Library of Medicine, and Web of Science were searched from inception to July 16, 2021. **Study Selection and Data Extraction:** Papers reporting individually documented humans on ibuprofen with hypokalemia, acidosis, or both were retained. Data were extracted using a checklist. **Data synthesis:** For the final analysis, we evaluated 41 reports describing 50 cases (26 males and 24 females; 36 adults and 14 children) with often profound hypokalemia, acidosis, or both after ingestion of ibuprofen. Twenty-six cases were acute and 24 chronic. Hypokalemia and acidosis occurred not only after ingestion of very high doses but also after ingestion of moderately high or even normal doses of ibuprofen. Laboratory values consistent with an excessive urinary potassium excretion or an altered urinary acidification were disclosed in 14 cases. Discontinuation of ibuprofen resulted in a resolution of hypokalemia and acidosis within days in 47 cases. The course was lethal in three cases. **Relevance to Patient Care and Clinical Practice:** This review highlights potentially fatal side effects of ibuprofen and can help doctors who are confronted with such a situation. **Conclusions:** These data highlight the potential of ibuprofen to occasionally induce hypokalemia and acidosis of renal origin. Discontinuation of ibuprofen results in a resolution within days.

Introduction

The propionic acid derivative ibuprofen in a dosage up to 30-40 mg/kg body weight daily, is a very popular and widely used nonselective nonsteroidal anti-inflammatory drug.[1] In many countries, this agent can be purchased without medical prescription, sometimes as fixed-drug combination with codeine.[1] In addition, these drugs lower renin secretion, consequently increasing potassium levels and potentiating the effect of antidiuretic hormone, also leading to a reduction in sodium levels and increasing renal tubular reabsorption of sodium, leading to fluid retention.

It is known since the middle of the 1980s that medication with ibuprofen may be associated with the development of hypokalemia and metabolic acidosis.[2] Although a few subsequent reports described subjects with hypokalemia, metabolic acidosis, or both hypokalemia and acidosis after the ingestion of ibuprofen, this association has never been systematically studied. The purpose of this report is to analyze the literature on this issue and to address the underlying pathophysiology.

Methods

Search Strategy

This review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations.[3] Searches were conducted in the databases of Excerpta Medica, the National Library of Medicine, and Web of Science on April 10, and repeated on July 16, 2021. Original reports with no date or language limits were considered. The search strategy incorporated the terms ibuprofen AND (acidosis OR hypokalemia). References listed within bibliographies of the retrieved records were also considered for inclusion.

Two of us independently screened all identified titles and abstracts in an unblinded fashion. Upon retrieval of candidate reports, full-text publications were reviewed for eligibility. During the entire process, uncertainties were solved through discussions and consensus. Institutional Review Board approval was not required for this literature review.

Eligibility criteria

We included original articles and letters reporting individually documented humans on ibuprofen with otherwise unexplained hypokalemia (<3.5 mmol/L), metabolic acidosis (pH <7.38 and bicarbonate <20 mmol/L), or both.

Data Extraction

Data were collected using a checklist and transcribed into a spreadsheet. The data extracted for each case meeting inclusion criteria were demographics, amount and duration of ibuprofen ingestion, co-medication (with emphasis for codeine, psychoactive and recreational drugs, proton pump inhibitors, and analgesics), clinical findings with emphasis on altered level of consciousness, muscle weakness or pain, and cardiac arrhythmias, and laboratory values with emphasis on circulating chloride, potassium, sodium, acid-base balance and creatinine, and urinary pH, chloride, potassium, sodium, creatinine and glucosuria. The management and course were also addressed.

Classification – completeness of reporting – analysis

Cases of hypokalemia, acidosis or both observed after ingestion of ibuprofen >40 mg/kg body weight daily were classified as intentional, accidental or dosage mistake. Cases

occurring after ingestion of ibuprofen for more than one week were considered chronic. Arousability and responsiveness to stimuli from the environment were used to roughly categorize the level of consciousness as normal, mildly to moderately impaired or severely impaired.[4]

In subjects with hypokalemia, a molar urine potassium over creatinine ratio >2.0 is indicative of an inappropriately elevated urinary potassium excretion.[5] On the other hand, in subjects with metabolic acidosis, a positive difference between the sum of the urine sodium plus potassium concentrations and the urine chloride concentration (i.e.: $Na^+ + K^+ - Cl^-$) is indicative of an impaired renal ammonium excretion ability.[5] Furthermore, in the context of acidosis, the inability to lower urinary pH <6.0 and the absence of glucosuria are considered distinctive features of renal acidosis of distal type.[6,7]

The sum of chloride and bicarbonate subtracted from sodium on blood was used to calculate blood anion gap and to further classify the cause of metabolic acidosis. Finally, the diagnosis of L-lactic acidosis was made in cases with metabolic acidosis and L-lactatemia >5.0 mmol/L.

Completeness of reporting was judged in consensus by two different authors for each included case using following two components: 1. detailed description of history, findings and course (rating 0 to 3); and 2. information on laboratory values and diagnostic work up (rating 0 to 3). The reporting quality was graded according to the sum of each item as excellent (5 to 6), good (3 to 4), or acceptable (2). Categorical data are presented as counts and were analyzed using the Fisher exact test. Continuous data are shown as medians and interquartile ranges and were compared using the Mann-Whitney-Wilcoxon test. Two-sided P-values of <0.05 were considered statistically significant.

Results

Search outputs – completeness of reporting

The study flowchart is shown in Figure 1. For the final analysis, we retained 41 scientific reports published since 1985: 22 from America (United States of America, N=20; Canada, N=1; Mexico, N=1), 12 from Europe (United Kingdom, N=9; Germany, N=2; Spain, N=1), six from Australia, and one from Asia (Saudi Arabia, N=1).[2, 8-47] Thirty-nine articles were published in English, one in Spanish, and one in German. The mentioned reports described 50 cases (14 children and 36 adults). The completeness in reporting was excellent in 19, good in 28 and acceptable in the remaining 3 cases.

Clinical and laboratory data at presentation

Dosage – acute and chronic ingestion

Hypokalemia or acidosis were observed in 44 (88%) patients receiving an excessive ibuprofen amount, i.e. more than 40 mg/kg body weight daily and in 6 (12%) subjects receiving a normal ibuprofen amount.

Twenty-six cases of hypokalemia, metabolic acidosis, or both hypokalemia and acidosis were considered acute.[2, 8-17, 19-21, 23, 25-27, 29-31, 37, 40, 43] Twenty-four were observed after a single dose of ibuprofen: 96 mg/kg in one case, 101 to 500 mg/kg in five cases, 501 to 1000 mg/kg in nine cases, >1000 mg/kg in eight cases (this information was not provided in one case). The remaining two cases ingested ibuprofen 28 mg/kg body weight daily, respectively 67 mg/kg body weight daily for three days or less.

The remaining twenty-four cases were considered chronic.[18, 22, 24, 28, 32-36, 38, 39, 41, 42, 44-47] Twenty-two cases were observed after ingestion of ibuprofen 40 mg/kg body weight or less

daily (N=5), 41-100 mg/kg body weight daily (N=6), or >100 mg/kg body weight daily (N=11). The duration of ingestion was two weeks (N=1), 1-3 months (N=8), 4-12 months (N=7), more than 12 months (N=3) and unspecified (but more than two weeks) in three cases. The remaining two cases received an unknown amount of ibuprofen for more than 12 months.

Demographics, clinical and laboratory features

Acute cases were more frequently males and children than chronic cases (table 1). Voluntary ingestion was the most common cause of ibuprofen ingestion in acute cases. These subjects usually presented with an altered level of consciousness, metabolic acidosis, and a rather severely impaired kidney function. Hypokalemia was rather uncommon in these cases. Chronic cases were mostly associated with ibuprofen dosage mistakes. These subjects usually presented with muscle weakness, hypokalemia, and metabolic acidosis. The kidney function was generally mildly impaired in these cases.

In addition to ibuprofen (table 1), various drugs had been administered in 28 cases.[11-13, 22-24, 26, 29-40, 42, 43, 45]

The renal tubular handling of potassium or acid-base balance was investigated in 19 cases. The urinary findings were consistent with an altered renal tubular function were noted in 14 of them (table 2).

Management - course

The management included ventilatory support, activated charcoal, gastric emptying, and the correction of hypokalemia in many cases (Table 1). Kidney replacement therapy, plasma exchange or extracorporeal membrane oxygenation were used in a minority of cases.

Three acute cases complicated by multiple organ failure died. At presentation, lactic acid was severely increased (17 and 30 mmol/L, respectively) in two of these cases (this parameter was not determined in the third case).

Some sequelae were observed in two chronic cases (mild kidney disease, N=1; hypokalemia and acidosis, N=1). The remaining 45 patients fully recovered within days with no differences between the two groups.

Discussion

It is widely accepted that nonselective nonsteroidal anti-inflammatory drugs, including among others ibuprofen, lower the renin secretion, thereby increasing potassium level, enhance the effect of antidiuretic hormone, thereby decreasing sodium level and may increase the renal tubular sodium reabsorption, thereby leading to fluid retention.[48-50] The present careful literature analysis documents 50 cases of hypokalemia or acidosis associated with the ingestion of ibuprofen. The discussion will focus on 1) the clinical presentation and the differences between acute and chronic cases; 2) the mechanisms underlying hypokalemia and acidosis; 3) the amount of ibuprofen associated with hypokalemia or acidosis, and 4) the suggested management.

In addition to an altered level of consciousness, a common feature in subjects with overdose of nonsteroidal anti-inflammatory drugs, the cases presented with symptomatic hypokalemia, acidosis, or both, often associated with impaired kidney function.[51-52] The severity of acidosis was similar in acute and chronic cases. In contrast, hypokalemia was more common and severe in chronic cases.

The urinary potassium excretion was inappropriately elevated in the patients with hypokalemia included in our analysis.[5] On the other hand, renal glucosuria was never observed. Furthermore, an inability to lower urinary pH below

6.0 was frequently noted.[5-7] Finally, signs consistent with an impaired urinary ammonium excretion were also observed.[5-7] It is therefore concluded that hypokalemia and acidosis were of renal (likely distal tubular) origin in the cases included in this analysis. The blood anion gap, which is usually normal in the context of hypokalemia and acidosis of renal origin, was higher in acute as compared with chronic cases. This observation suggests that further factors may have contributed to the development of metabolic acidosis in many cases, including accumulation of lactic acid or fasting ketosis.

The mechanisms by which ingestion of ibuprofen may impair the renal ability to reduce potassium and increase ammonium excretion remain speculative. It is usually assumed that ingestion of ibuprofen at doses ≤100 mg/kg daily does not cause any symptoms. Furthermore, serious symptoms are not expected until doses of ≥200 mg/kg daily and life-threatening toxicity generally occurs at ingested doses ≥400 mg/kg body weight daily.[51-52] Interestingly, this analysis reveals that hypokalemia and acidosis occur also in patients ingesting a normal amount of this agent (less than 40 mg/kg body weight daily) and in cases ingesting a "non-toxic" amount ranging from 40 to 100 mg/kg body weight daily. Concerning the 5 cases reported with doses lower than 40 mg/kg daily: one case ingested the codeine formulation, one case ingested paracetamol, esomeprazole, and a psychoactive drug together and the remaining three cases just ibuprofen. Hypokalemia and acidosis were never reported in subjects on treatment with frequently prescribed nonselective nonsteroidal anti-inflammatory drugs such as arylacetic acid derivatives (e.g. diclofenac), acetic acid derivatives (e.g. indomethacin) and oxicams (e.g. piroxicam) and in patients prescribed selective nonsteroidal anti-inflammatory drugs.[50] In contrast, hypokalemia was noted not only after ingestion of ibuprofen but also in one patient on treatment with naproxen.[53] Since

both ibuprofen and naproxen are propionic acid derivatives, it is tempting to assume that hypokalemia and acidosis occur uniquely on treatment with the mentioned class of nonsteroidal anti-inflammatory drugs.[50] Finally, considering the rarity of this biochemical abnormality, it has been speculated that it occurs exclusively in predisposed subjects. Of note, the biochemical abnormalities occasionally observed after ibuprofen resemble those observed on medication with a carbonic anhydrase inhibitor such as acetazolamide or topiramate.[54]

The management of hypokalemia and acidosis caused by ibuprofen is the same as that for poisoning for all nonsteroidal anti-inflammatory drugs. A severely impaired level of consciousness may require ventilatory support, fluids and vasopressors may be advised for hypotension.[51-52] Gastrointestinal decontamination with charcoal is advised for acute cases.[55] Supportive treatment is indicated for correction of hypokalemia and altered fluid balance. Furthermore, most authorities advise crystalloid and potassium to correct volume depletion and hypokalemia. Bicarbonate therapy is not recommended because it aggravates hypokalemia.[56-57] Removal of ibuprofen via kidney replacement therapy, plasma exchange or extracorporeal membrane oxygenation is not necessary in the vast majority of cases.[51-52] Kidney replacement therapy is required in cases with severe kidney injury.

The most important limitation of this systematic review arises from the small number of published reports on hypokalemia or acidosis associated with ibuprofen ingestion. Furthermore, completeness in reporting cases was sometimes rather low. Finally, since therapeutic suggestions can be uneasily inferred by cumulating individual case reports, suggested treatment recommendations were extrapolated from the general literature on ibuprofen overdose and electrolyte or acid-base disturbances. The major strength of this review is

that it is the first to investigate the clinical-biochemical features and pathophysiology on hyperkalemia and metabolic acidosis induced by ibuprofen.

Relevance to Patient Care and Clinical Practice

This literature review highlights rare but potentially fatal side effects of one of the world's most widely used pain medications ibuprofen. Such a review can certainly help many physicians around the world who face an emergency with a patient with severe hypokalemia and metabolic acidosis and is unique.

Conclusions

This literature review highlights the potential of acute and chronic ingestion of ibuprofen to occasionally induce profound hypokalemia and acidosis of renal origin. Contrary to what common sense would dictate, these biochemical abnormalities occur not only after ingestion of very high doses but also after ingestion of moderately high or even normal doses of ibuprofen. Discontinuation of ibuprofen normally results in complete biochemical resolution within days.

Declarations

Conflict of interest

The authors declare that they have no conflict of interest.

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References

1. Davies NM. Clinical pharmacokinetics of ibuprofen. The first 30 years. Clin Pharmacokinet. 1998;34(2):101-154. https://doi.org/10.2165/00003088-199834020-00002. PMID: 9515184.

2. Bennett RR, Dunkelberg JC, Marks ES. Acute oliguric renal failure due to ibuprofen overdose. South Med J. 1985;78(4):490-491. https://doi.org/10.1097/00007611-198504000-00036.

3. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. J Clin Epidemiol. 2021;134:178-189. doi: 10.1016/j.jclinepi.2021.03.001.

4. Holland J, Brown E. Acute presentation of altered conscious state. Paediatr Child Health. 2021;31(4):153-162.

5. Kamel KS, Halperin ML. Use of urine electrolytes and urine osmolality in the clinical diagnosis of fluid, electrolytes, and acid-base disorders. Kidney Int Rep. 2021;6(5):1211-1224. https://doi.org/10.1016/j.ekir.2021.02.003.

6. Santos F, Ordóñez FA, Claramunt-Taberner D et al. Clinical and laboratory approaches in the diagnosis of renal tubular acidosis. Pediatr Nephrol. 2015;30(12):2099-2107. https://doi.org/10.1007/s00467-015-3083-9.

7. Trepiccione F, Walsh SB, Ariceta G, et al. Distal renal tubular acidosis: ERKNet/ESPN clinical practice points. Nephrol Dial Transplant. 2021;36(9):1585-1596. https://doi.org/10.1093/ndt/gfab171.

8. Lee CY, Finkler A. Acute intoxication due to ibuprofen overdose. Arch Pathol Lab Med. 1986;110(8):747-749.

9. Linden CH, Townsend PL. Metabolic acidosis after acute ibuprofen overdosage. J Pediatr. 1987;111(6 Pt 1):922-925. https://doi.org/10.1016/s0022-3476(87)80220-2.

10. Primos W, Bhatnager A, Bishop P, et al. Acute metabolic acidosis due to ibuprofen overdose. J Miss State Med Assoc. 1987;28(9):233-234.

11. Perazella MA, Buller GK. Can ibuprofen cause acute renal failure in a normal individual? A case of acute overdose. Am J Kidney Dis. 1991;18(5):600-602. https://doi.org/10.1016/s0272-6386(12)80657-3.

12. Downie A, Ali A, Bell D. Severe metabolic acidosis complicating massive ibuprofen overdose. Postgrad Med J. 1993;69(813):575-577. https://doi.org/10.1136/pgmj.69.813.575.

13. Le HT, Bosse GM, Tsai Y. Ibuprofen overdose complicated by renal failure, adult respiratory distress syndrome, and metabolic acidosis. J Toxicol Clin Toxicol. 1994;32(3):315-320. https://doi.org/10.3109/15563659409017966.

14. Kim J, Gazarian M, Verjee Z, Johnson D. Acute renal insufficiency in ibuprofen overdose. Pediatr Emerg Care. 1995;11(2):107-108. https://doi.org/10.1097/00006565-199504000-00013.

15. Zuckerman GB, Uy CC. Shock, metabolic acidosis, and coma following ibuprofen overdose in a child. Ann Pharmacother. 1995;29(9):869-871. https://doi.org/10.1177/106002809502900908.

16. Al-Harbi NN, Domrongkitchaiporn S, Lirenman DS. Hypocalcemia and hypomagnesemia after ibuprofen overdose. Ann Pharmacother. 1997;31(4):432-434. https://doi.org/10.1177/106002809703100408.

17. Ritter A, Eskin B. Ibuprofen overdose presenting with severe agitation and hypothermia. Am J Emerg Med.

1998;16(5):549-550. https://doi.org/10.1016/s0735-6757(98)90020-1.

18. Gaul C, Heckmann JG, Druschky A, et al. Renale tubuläre Azidose mit schwerer hypokaliämischer Tetraparese nach Ibuprofeneinnahme [Renal tubular acidosis with severe hypokalemic tetraparesis after ibuprofen intake]. Dtsch Med Wochenschr. 1999;124(16):483-486. https://doi.org/10.1055/s-2007-1024347.

19. Easley RB, Altemeier WA 3rd. Central nervous system manifestations of an ibuprofen overdose reversed by naloxone. Pediatr Emerg Care. 2000;16(1):39-41. https://doi.org/10.1097/00006565-200002000-00012.

20. Oker EE, Hermann L, et al. Serious toxicity in a young child due to ibuprofen. Acad Emerg Med. 2000;7(7):821-823. https://doi.org/10.1111/j.1553-2712.2000.tb02278.x.

21. Seifert SA, Bronstein AC, McGuire T. Massive ibuprofen ingestion with survival. J Toxicol Clin Toxicol. 2000;38(1):55-57. https://doi.org/10.1081/clt-100100917.

22. Chetty R, Baoku Y, Mildner R, et al. Severe hypokalaemia and weakness due to Nurofen misuse. Ann Clin Biochem. 2003;40(Pt 4):422-423. https://doi.org/10.1258/000456303766477101.

23. Dyer BT, Martin JL, Mitchell JL, et al. Hypokalaemia in ibuprofen and codeine phosphate abuse. Int J Clin Pract. 2004;58(11):1061-1062. https://doi.org/10.1111/j.1368-5031.2004.00304.x.

24. Lambert AP, Close C. Life-threatening hypokalaemia from abuse of Nurofen Plus. J R Soc Med. 2005;98(1):21. https://doi.org/10.1258/jrsm.98.1.21.

25. Wood DM, Monaghan J, Streete P, et al. Fatality after deliberate ingestion of sustained-release ibuprofen: a case

report. Crit Care. 2006;10(2):R44. https://doi.org/10.1186/cc4850.

26. Holubek W, Stolbach A, Nurok S et al. A report of two deaths from massive ibuprofen ingestion. J Med Toxicol. 2007;3(2):52-55. doi: 10.1007/BF03160908.

27. Marciniak KE, Thomas IH, Brogan TV, et al. Massive ibuprofen overdose requiring extracorporeal membrane oxygenation for cardiovascular support. Pediatr Crit Care Med. 2007;8(2):180-182. https://doi.org/10.1097/01.PCC.0000257036.26436.42.

28. Ter A, Salha R, Vadamalai V, et al. Ibuprofen codeine combination precipitating severe hypokalaemia in a patient with pre-existing type 1 renal tubular acidosis. NDT Plus. 2008;1(4):270-271. https://doi.org/10.1093/ndtplus/sfn025.

29. Lamkin S, Fraiz A. An acid/base disturbance from ibuprofen toxicity. J Emerg Nurs. 2009;35(6):584-585. https://doi.org/10.1016/j.jen.2009.07.012.

30. Ernest D, Chia M, Corallo CE. Profound hypokalaemia due to Nurofen Plus and Red Bull misuse. Crit Care Resusc. 2010;12(2):109-110.

31. Levine M, Khurana A, Ruha AM. Polyuria, acidosis, and coma following massive ibuprofen ingestion. J Med Toxicol. 2010;6(3):315-317. https://doi.org/10.1007/s13181-010-0076-8.

32. Mallett A, Lynch M, John GT, et al. Ibuprofen-related renal tubular acidosis in pregnancy. Obstet Med. 2011;4(3):122-124. https://doi.org/10.1258/om.2011.110041.

33. Ng JL, Morgan DJ, Loh NK, et al. Life-threatening hypokalaemia associated with ibuprofen-induced renal tubular acidosis. Med J Aust. 2011;194(6):313-316. https://doi.org/10.5694/j.1326-5377.2011.tb02982.x.

34. Page CB, Wilson PA, Foy A, et al. Life-threatening hypokalaemia associated with ibuprofen-induced renal tubular acidosis. Med J Aust. 2011;194(11):614. https://doi.org/10.5694/j.1326-5377.2011.tb03123.x.

35. Blackstock MJ, Lee A. Hypokalaemia and renal tubular acidosis due to abuse of Nurofen plus. Case Rep Crit Care. 2012;2012:141505. https://doi.org/10.1155/2012/141505.

36. Salter MD. Ibuprofen-induced hypokalemia and distal renal tubular acidosis: a patient's perceptions of over-the-counter medications and their adverse effects. Case Rep Crit Care. 2013;2013:875857. https://doi.org/10.1155/2013/875857.

37. Arens A, Smollin C. Case files of the University of California, San Francisco Medical Toxicology Fellowship: Seizures and a persistent anion gap metabolic acidosis. J Med Toxicol. 2016;12(3):309-314. https://doi.org/10.1007/s13181-016-0547-7.

38. Dang MH, Wu S, Sia C. Ibuprofen-induced renal tubular acidosis-a rare cause of rhabdomyolysis: a case report. Oxf Med Case Reports. 2016;2016(8):omw057. https://doi.org/10.1093/omcr/omw057.

39. Bichard L, Toh D. Ibuprofen-induced distal (type 1) renal tubular acidosis and hypokalaemia: the dangers of ibuprofen-codeine combination over-the-counter preparations. Intern Med J. 2017;47(6):707-709. https://doi.org/10.1111/imj.13436.

40. Geith S, Renner B, Rabe C, et al. Ibuprofen plasma concentration profile in deliberate ibuprofen overdose with circulatory depression treated with therapeutic plasma exchange: a case report. BMC Pharmacol Toxicol. 2017;18(1):81. https://doi.org/10.1186/s40360-017-0187-9.

41. Chávez-Iñiguez JS, Espinosa-García F, Pacheco-Plascencia A, et al. The Case - Severe hypokalemia and metabolic

acidosis. Kidney Int. 2018;93(5):1255-1256. https://doi.org/10.1016/j.kint.2017.10.010.

42. Patil S, Subramany S, Patil S, et al. Ibuprofen abuse - a case of rhabdomyolysis, hypokalemia, and hypophosphatemia with drug-induced mixed renal tubular acidosis. Kidney Int Rep. 2018;3(5):1237-1238. https://doi.org/10.1016/j.ekir.2018.05.014.

43. Habimana-Jordana A, López-Corominas V, Barceló-Martín B, et al. Acidosis metabólica láctica como manifestación de intoxicación voluntaria en adolescentes [Metabolic lactic acidosis as a sign of voluntary poisoning in adolescents]. An Pediatr (Barc). 2019;90(2):121-123. https://doi.org/10.1016/j.anpedi.2018.02.024.

44. Li R, Hasan N, Armstrong L, et al. Impaired consciousness, hypokalaemia and renal tubular acidosis in sustained Nurofen Plus abuse. BMJ Case Rep. 2019;12(11):e231403. https://doi.org/10.1136/bcr-2019-231403.

45. Thammineni N, Kathi PR, Sharma A, et al. Ibuprofen overuse leading to life-threatening hypokalemia associated with renal tubular acidosis in two patients. Cureus. 2019;11(12):e6404. https://doi.org/10.7759/cureus.6404.

46. Chhabria M, Portales-Castillo I, Chowdhury M, et al. A Case of Severe Hypokalemia. Am J Kidney Dis. 2020;76(1):A9-A12. https://doi.org/10.1053/j.ajkd.2019.12.020.

47. Mandal AKJ, Howarth H, Jordaan JAJ, et al. Ibuprofen-Induced Distal Renal Tubular Acidosis and Hyporeninemic Hypoaldosteronism: Enough NSAID. Mayo Clin Proc. 2020;95(10):2296-2299. https://doi.org/10.1016/j.mayocp.2020.08.009.

48. Hart FD, Huskisson EC. Non-steroidal anti-inflammatory drugs. Current status and rational therapeutic use. Drugs.

1984;27(3):232-255. https://doi.org/10.2165/00003495-198427030-00004.

49. Clive DM, Stoff JS. Renal syndromes associated with nonsteroidal antiinflammatory drugs. N Engl J Med. 1984;310(9):563-572. https://doi.org/10.1056/NEJM198403013100905.

50. Dunn M. The role of arachidonic acid metabolites in renal homeostasis. Non-steroidal anti-inflammatory drugs renal function and biochemical, histological and clinical effects and drug interactions. Drugs. 1987;33 Suppl 1:56-66. https://doi.org/10.2165/00003495-198700331-00009.

51. Zecca TC. Management of ibuprofen overdose. Pediatr Rev. 1997;18(3):107. https://doi.org/10.1542/pir.18-3-107.

52. Volans G, Monaghan J, Colbridge M. Ibuprofen overdose. Int J Clin Pract Suppl. 2003;(135):54-60.

53. Lua J, Bellamy CO, Whitworth C, et al. An under-recognized cause of CKD. Am J Kidney Dis. 2011;58(4):A30-A33. https://doi.org/10.1053/j.ajkd.2011.04.026.

54. Dell'Orto VG, Belotti EA, Goeggel-Simonetti B, et al. Metabolic disturbances and renal stone promotion on treatment with topiramate: a systematic review. Br J Clin Pharmacol. 2014;77(6):958-964. https://doi.org/10.1111/bcp.12283.

55. Heard K. The changing indications of gastrointestinal decontamination in poisonings. Clin Lab Med. 2006;26(1):1-12. https://doi.org/10.1016/j.cll.2006.01.001.

56. Aschner JL, Poland RL. Sodium bicarbonate: basically useless therapy. Pediatrics. 2008;122(4):831-835. https://doi.org/10.1542/peds.2007-2400.

57. Kraut JA, Kurtz I. Treatment of acute non-anion gap metabolic acidosis. Clin Kidney J. 2015;8(1):93-99. https://doi.org/10.1093/ckj/sfu126.

Table 1

Table 1: Clinical and laboratory data in patients with both metabolic acidosis and hypokalemia (N=25), isolated metabolic acidosis (N=22) or isolated hypokalemia (N=3) associated with acute and chronic ibuprofen ingestion. Continuous data are shown as medians and interquartile ranges, categorical data as frequency.

	All	Acute	Chronic	P-value
N	50	26	24	
Demographics				
Males : females	26 : 24	18 : 8	8 : 16	<0.02
Age, years	35 [17-45]	17 [4-36]	39 [35-46]	<0.0001
≤18 years	14	14	0	<0.0001
No ibuprofen overdose, N	6	1	5	0.093
Ibuprofen overdose, N	44	25	19	
Intentional	18	15	3	<0.005
Accidental	8	8	0	<0.005
Dosage mistake	16	1	15	<0.0001
Cause unknown	2	1	1	0.132
Co-medication				
None, N	22	15	7	0.052
Codeine, N	16	2	14	<0.0001
Psychoactive drugs, N	14	6	8	0.533
Recreational drugs, N	7	4	3	0.999
Proton pump inhibitors, N	6	1	5	0.093
Analgesics, N	5	2	3	0.661
Antihistamines, N	4	1	3	0.340
Valproic acid, N	1	1	0	0.999
Clinical presentation				
Level of consciousness altered	22	17	5	<0.0005
Mildly-moderately impaired	10	6	4	

Severely impaired	12	11	1	
Muscle weakness or pain	23	4	19	<0.0001
Without rhabdomyolysis	14	2	12	
With rhabdomyolysis	9	2	7	
Cardiac arrhythmias	16	5	11	0.068
Blood values				
Potassium				
mmol/L	2.3 [1.8-4.1]	4.2 [4.0-4.9]	1.8 [1.0-2.0]	<0.0001
<3.5 mmol/L	28	4	24	
3.0-3.4 mmol/L, N	1	1	0	
2.5-2.9 mmol/L, N	3	0	3	
<2.5 mmol/L, N	24	3	21	
>5.0 mmol/L, N	4	4	0	0.103
Bicarbonate				
mmol/L	13 [11-17]	13 [9-17]	14 [11-16]	0.850
<20 mmol/L, N	48	25	23	
15-19 mmol/L, N	17	8	9	
10-14 mmol/L, N	18	6	12	
<10 mmol/L, N	10	7	3	
Lactic acid >5.0 mol/L, N	6	5	1	0.103
Sodium				
mmol/L	140 [137-141]	140 [138-141]	141 [137-141]	0.623
<135 mmol/L	7	4	3	
>145 mmol/L	4	2	2	
Chloride	111 [106-116]	106 [104-109]	114 [111-120]	<0.0001
Anion gap[+]	14 [11-18]	19 [16-22]	12 [10-14]	<0.0001
Creatinine, µmol/L	106 [83-206]	170 [95-247]	96 [77-103]	<0.02
Management				
Ventilatory support, N	12	11	1	<0.005
Activated charcoal, N	14	14	0	<0.0001
Gastric emptying, N	12	12	0	<0.0001
Potassium, N	22	3	19	<0.0001
Alkali, N	20	14	6	<0.05
Further management, N	6	6*	0	<0.05

Course				
Death, N	3	3	0	0.2359
Sequelae, N	2	0	2**	0.2253
Full recovery, N	45	23	22	0.9999

[+] sum of chloride and bicarbonate subtracted from sodium; * kidney replacement therapy (N=4), extracorporeal membrane oxygenation and plasma exchange (N=1), plasma exchange (N=1); ** mild chronic kidney disease (N=1); hypokalemia and acidosis (N=1).

Table 2

Table 2: Urinary findings indicative of a disturbed renal tubular function in patients with acute and chronic ibuprofen ingestion. Continuous data are shown as medians and interquartile ranges.

	All (N=50)	**Acute (N=26)**	**Chronic (N=24)**
pH ≥6.0, N	14	0	14
Increased potassium excretion*, N	8	1	7
Apparently impaired ammonium excretion◆, N	7	1	6
Renal glucosuria, N	0	0	0

* molar potassium over creatinine ratio higher than 2.0; ◆ sum of urinary potassium and sodium level higher than chloride.

Figure 1 - Legend

Ibuprofen-associated hypokalemia and metabolic acidosis. Flowchart of the literature search process.

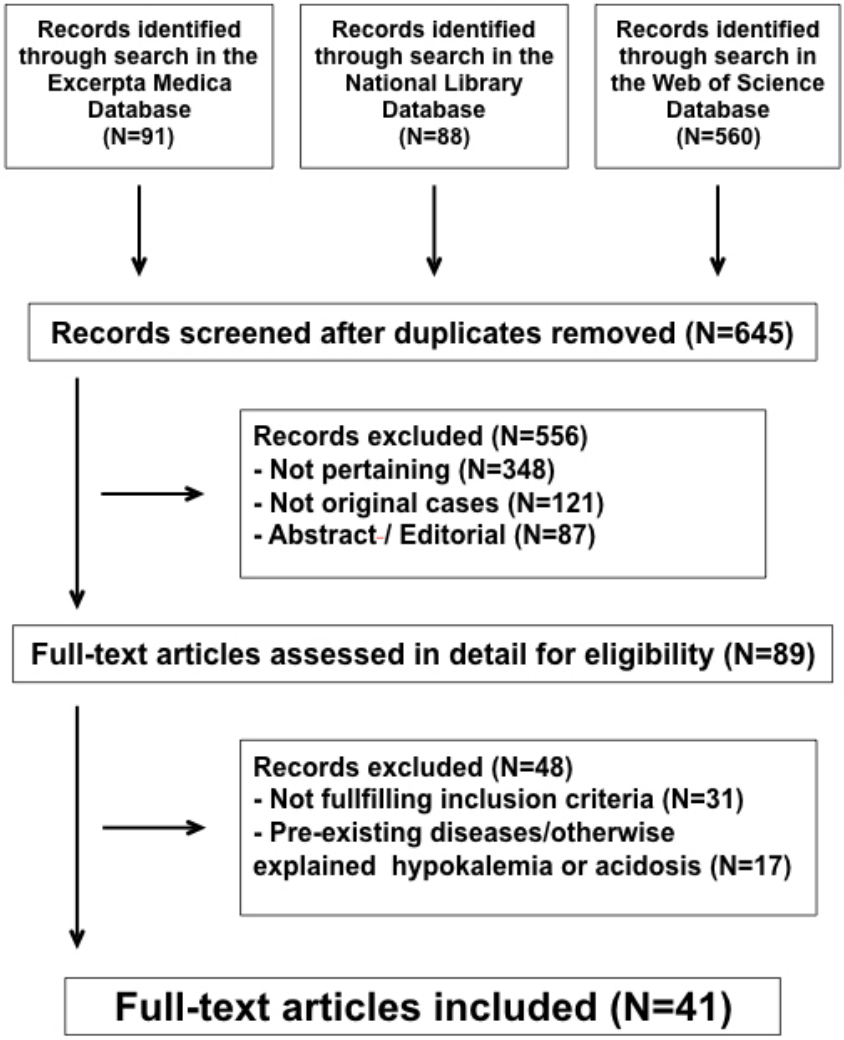

Figure 1