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CASE REPORT

Apixaban overdose in children: case report and proposed management. A brief communication from the Pediatric and Neonatal Thrombosis and Hemostasis SSC of ISTH

Meredith Wiggins[1,2] | Tina Biss[3] | Leslie Raffini[4] | Heleen Van Ommen[5] | Anthony Chan[6] | Christina Vanderpluym[7] | Neil Goldenberg[8] | Paul Monagle[1,9]

[1]Sydney Children's Hospital, Randwick, Sydney, New South Wales, Australia

[2]University of New South Wales, Sydney, New South Wales, Australia

[3]Newcastle upon Tyne Hospitals, National Health Service Trust, Newcastle upon Tyne, United Kingdom

[4]Department of Pediatrics, Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, Pennsylvania, USA

[5]Sophia Children's Hospital Erasmus University Medical Center, Rotterdam, The Netherlands

[6]Department of Pediatrics, McMaster Centre for Transfusion Research, McMaster University, McMaster Children's Hospital, Hamilton, Ontario, Canada

[7]Heart Center, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts, USA

[8]Departments of Pediatrics and Medicine, Johns Hopkins University School of Medicine, Johns Hopkins All Children's Hospital, St. Petersburg, Florida, USA

[9]University of Melbourne, Melbourne, Victoria, Australia

Correspondence
Meredith Wiggins, Sydney Children's Hospital, Randwick, NSW 2031, Australia.
Email: Meredith.wiggins@health.nsw.gov.au

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Abstract

Background: Direct oral anticoagulants are commonly prescribed for adults and increasingly also for children requiring anticoagulation therapy. While household medications should not be accessible to children, accidental, and intentional overdoses occur.

Key Clinical Question: How should apixaban overdose in children be managed?.

Clinical Approach: We present a case of an accidental overdose with the factor Xa antagonist apixaban in a young child and propose an approach to the management of cases of apixaban overdose in children.

Conclusion: Given the increasing use of direct oral anticoagulants, it is important to have an approach to the management of overdose of these medications.

KEYWORDS
anticoagulants, apixaban, child, drug overdose, pediatrics

Essentials

- Direct oral anticoagulant drugs such as apixaban are increasingly being prescribed.
- Safety information on overdose of apixaban in children is important.
- We discuss a case of apixaban overdose in a young child.
- Recommendations for management of apixaban overdose in children are provided.

A previously well 18-month-old boy (weight 13.1 kg) presented to his local hospital emergency department approximately 2 hours after accidental ingestion of his grandmother's medication. Twenty-four milligrams of candesartan and 40 mg of apixaban were unaccounted for.

On examination, the child was alert and appeared well. Vital signs were normal, with normal blood pressure. There was no evidence of bleeding. Initial coagulation studies collected 2.5 hours post ingestion were significantly abnormal (Table). Hemoglobin and renal function were normal. Activated charcoal was not recommended by the poisons advisory service. Our tertiary children's hospital was consulted approximately 6 hours post ingestion. The patient was transferred for further monitoring. Repeat coagulation studies, approximately 12 hours postingestion, showed marked improvement. The child remained well, and at 24 hours, his coagulation studies had normalized. An apixaban level taken at this time was 88 ng/mL, and he was discharged from hospital.

Two previous case reports of apixaban overdose in children have been published. Launay et al. [1] described a 40 mg ingestion in a 23-month-old (12.9 kg) child, and Ha et al. [2] reported a 15 mg ingestion in an 8-month-old (11 kg) infant. Only the latter received activated charcoal. As in our patient, prothrombin time and activated partial thromboplastin time were significantly prolonged within the first 6 hours of ingestion and then gradually improved over the subsequent 24 hours. In the case described by Launay et al. [1], apixaban levels peaked at 1712 ng/mL, with a small amount of drug still detected 48 hours after postingestion. Neither patient had any bleeding.

The absence of bleeding in our patient and other reported cases may be due to the short half-life of apixaban (~12 hours) and wide therapeutic range. Predicted Cmax with a 5 mg dose twice a day in adult patients is 132 ng/mL (59-321 ng/mL) [3]. Prothrombin time and activated partial thromboplastin time assays are relatively insensitive to apixaban and are usually normal, even with therapeutic drug levels [4]. The markedly abnormal coagulation studies seen in these cases indicate a significant drug ingestion. Chromogenic anti-Xa levels show a linear relationship to apixaban plasma concentration [5].

Administration of activated charcoal up to 6 hours post ingestion has been shown to reduce apixaban absorption in healthy individuals by up to 50% [6]. Adult guidelines recommend further treatment only if clinically significant bleeding occurs [7]. Options to attempt to achieve hemostasis include the specific reversal agent andexanet alfa, prothrombin complex concentrate, or activated prothrombin complex concentrate. Andexanet alfa is not readily available in many centers, and there are no published data on dosing, safety, or efficacy in children [8].

The following (Figure) is a proposed plan for management of apixaban overdose in children, based on available evidence [6,7,8] and expert opinion of the authors:

TABLE Serial coagulation results for an 18-month-old boy following ingestion of 40 mg apixaban.

Time postingestion	2 Hours	12 Hours	24 Hours
PT (s) (normal range, 9-13 s)	38.7	16	11.9
INR	3.3	1.4	1.1
aPTT (s) (normal range, 25-37 s)	53	43.9	34.4
Apixaban level (ng/mL)			88

aPTT, activated partial thromboplastin time; INR, international normalized ratio; PT, prothrombin time.

FUNDING

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ETHICS STATEMENT

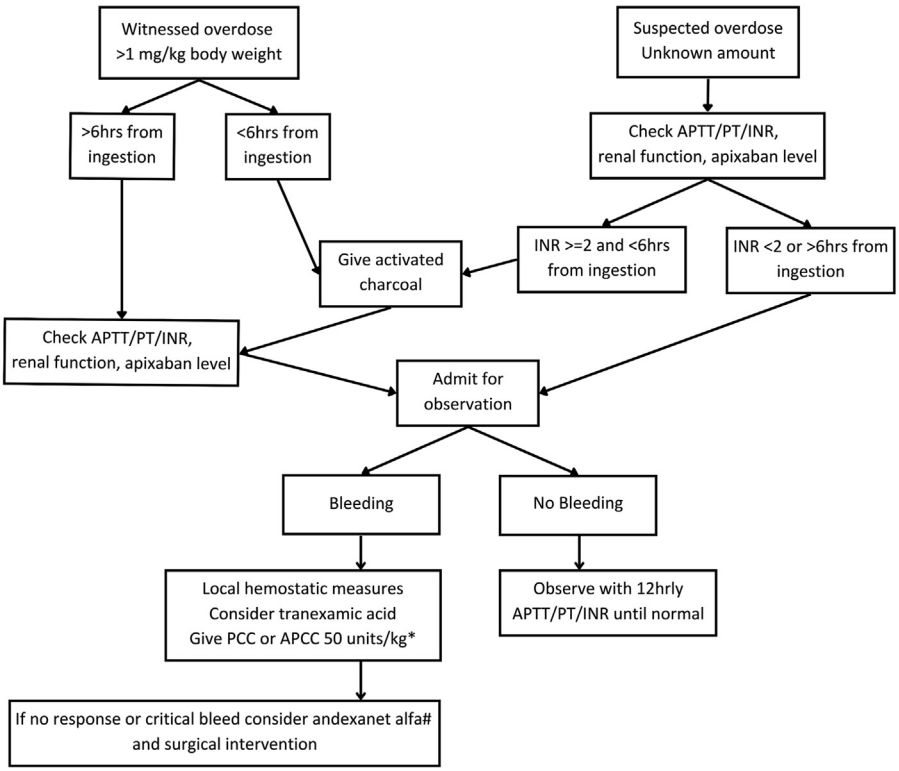
This case report has ethics approval from the Sydney Children's Hospital ethics committee.

AUTHOR CONTRIBUTIONS

M.W. wrote the case report with coauthors contributing to the proposed management plan for apixaban overdose.

RELATIONSHIP DISCLOSURE

M.W. has no conflicts of interest to declare. T.B. had received honoraria from Bayer and Hartley Taylor Medical Communications. L.R. has been on the advisory board for Janssen and Boehringer Ingelheim. H.v.O. has received research funding from Octapharma and Bayer BV; is a consultant for Boehringer Ingelheim for a dabigatran phase 4 study and Bayer BV for an asundexian study; and has received sponsorship from Xenios for a lecture. A.C. has received research funding from Novo Nordisk, AceAge, C17, I-ACT, and the Canadian Hemophilia Society; has been involved in clinical trials for Bayer, Pfizer, Daiichi, Sanofi, Sobi, Novo Nordisk, and Takeda; is on advisory boards for Takeda and Novo Nordisk and steering committees for Bayer and Daiichi Sankyo; and has received honoraria from Bayer, Novo Nordisk, Takeda, and Roche. C.V. is on the scientific advisory committee for the Merck veriguciat trial and has been a consultant for Astra Zeneca. N.G. is chair of the Pediatric/Neonatal Thrombosis and



*PCC- prothrombin complex concentrate, APCC- activated prothrombin complex concentrate; choice depends on local practice/availability
#There is no published data on the safety of andexanet alfa in children

FIGURE Apixaban overdose management algorithm

Haemostasis Scientific and Standardization Committee, International Society on Thrombosis and Haemostasis (ISTH); has received research funding from the National Institutes of Health National Heart Lung and Blood Institute, Boehringer Ingelheim, and Chiesi; has been a consultant for Anthos, Bayer, Daiichi Sankyo, and Janssen; and has been on the data and safety monitoring committee for pediatric apixaban trials and for Novartis allergy trials. P.M. was on the steering committee for the Saxophone and Einstein Junior clinical trials and is involved in the American Society of Hematology haemostasis thrombosis working group, ISTH guidelines and guidance committee, and Pedi Atlas.

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