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CLINICAL RESEARCH

Web-based Application for the Population Pharmacokinetic Service (WAPPS)'s impact on dosage selection: a single paediatric centre experience

Celia Kwan, Mihir D. Bhatt, Karen Strike, Kay Decker, Davide Matino, Anthony K.C. Chan

Background: Current treatment for severe haemophilia includes prophylactic factor replacement to prevent bleeding. Coagulation factor products have significant inter-patient variability in pharmacokinetic (PK) parameters. Optimal management requires tailoring prophylaxis to individual PK parameters. Web-based Application for the Population Pharmacokinetic Service (WAPPS) is a tool that estimates individual PK values using a population approach. Despite its growing use to help guide dosing selection, few studies have investigated its clinical impact. **Aim:** To investigate any change in prophylaxis regimen and hours per week where factor level is under 1%, pre- and post-PK testing using WAPPS, for paediatric patients with severe haemophilia. **Methods:** A retrospective chart review

CELIA KWAN
Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada

MIHIR D. BHATT
Department of Paediatrics, McMaster University, Hamilton, ON, Canada; Hamilton Niagara Regional Hemophilia Program, McMaster Children's Hospital, Hamilton Health Sciences, Hamilton, ON, Canada

KAREN STRIKE
Hamilton Niagara Regional Hemophilia Program, McMaster Children's Hospital, Hamilton Health Sciences, Hamilton, ON, Canada; School of Rehabilitation Science, Faculty of Health Science, McMaster University, Hamilton, ON, Canada

KAY DECKER
Hamilton Niagara Regional Hemophilia Program, McMaster Children's Hospital, Hamilton Health Sciences, Hamilton, ON, Canada

DAVIDE MATINO
Hamilton Niagara Regional Hemophilia Program, McMaster Children's Hospital, Hamilton Health Sciences, Hamilton, ON, Canada; Department of Medicine, McMaster University, Hamilton, ON, Canada

ANTHONY K.C. CHAN
Department of Paediatrics, McMaster University, Hamilton, ON, Canada; Hamilton Niagara Regional Hemophilia Program, McMaster Children's Hospital, Hamilton Health Sciences, Hamilton, ON, Canada.
Email: akchan@mcmaster.ca.

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A recent study at McMaster Children's Hospital concludes that using WAPPS-generated pharmacokinetic data to personalise prophylaxis recommendations both validates clinical practice and supports patient-centred care

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was conducted for all paediatric patients with severe haemophilia receiving care between April 2013 and July 2018 at McMaster Children's Hospital who have used WAPPS. Data extracted included: patient demographics, PK data generated by WAPPS, prophylaxis regimen pre- and post-PK testing, and reason for regimen change. The number of hours per week where factor level was under 1% pre- and post-PK testing was calculated using WAPPS. **Results:** Thirty-one patients were included; 42% (n=13) changed their prophylaxis regimen after PK testing. After using PK data to personalise prophylaxis recommendations, there was a decrease in the number of hours per week where factor level is under 1% (from an average of 13.1 hours/week to 11.8 hours/week), though not statistically significant (p=0.16). **Conclusion:** PK data generated by WAPPS has direct impact by informing changes to prophylaxis recommendations. This individualised approach promotes patient-centred care and patient engagement without increasing the time spent with factor levels below 1%. It also confirms and validates clinical practice.

Keywords: *haemophilia A, haemophilia B, factor VIII, factor IX, children, pharmacokinetics*

Haemophilia is a bleeding disorder caused by a deficiency in coagulation factors, specifically factor VIII (FVIII) in haemophilia A, and factor IX (FIX) in haemophilia B. Based on the clotting factor levels, haemophilia can be classified as mild (factor levels >5%), moderate (factor levels between 1-5%), or severe (factor levels <1%). Those with severe haemophilia are at risk of spontaneous bleeding into their joints and soft tissues, which can lead to arthropathy [1]. Current treatment for severe haemophilia includes prophylactic factor replacement to prevent bleeding and joint damage [1]. Compared to on-demand treatment, prophylactic treatment has been shown to reduce all bleeding, including hemarthroses [2]. However, coagulation factor products have significant inter-patient variability in pharmacokinetic (PK) parameters [3]. The half-life of FVIII, for instance, can vary from 7 to 21 hours as per a population study in patients between the ages of 7 and 74 [4]. Hence, patients receiving the same amount of FVIII can have very different trough FVIII and time per week where FVIII is below a certain level [3]. Optimal haemophilia management, therefore, requires tailoring prophylaxis to individual PK parameters [5]. This tailored approach has been suggested to have increased clinical benefit [6].

AIM

The Web-based Application for the Population Pharmacokinetic Service (WAPPS) is a tool that estimates individual PK values for factor concentrates using a population approach [5]. Despite its growing use to help guide dosing selection, literature investigating its clinical impact is scarce [7]. The purpose of our study is to conduct a single centre retrospective review to investigate whether, for patients with haemophilia under the age of 18, there is a change before and after PK testing using WAPPS in: 1) prophylaxis regimen and 2) number of hours per week in which the blood measurement of FVIII is under 1%.

METHODS

A retrospective chart review at McMaster Children's Hospital was conducted for all patients with haemophilia (A and B) under 18 years of age between April 2013 and July 2018 who have used WAPPS. Data extracted included: patient demographics (age, weight, height, baseline factor level), pharmacokinetic (PK) data generated by WAPPS ('balanced' estimates), prophylaxis regimen pre- and post-PK testing, and reason for changing (or not changing) the regimen if available (Table 1). The number of hours per week in which the blood measurement of FVIII was under 1% before and after PK testing was calculated using the clinical calculator in WAPPS. Statistical analysis was performed using the Microsoft Excel Program, Office 365 version (Microsoft, Redmond, Washington, USA). For FVIII, our centre aimed to collect samples for PK estimate at 4 hours, 24 hours and 48 hours post-infusion. The alternative would be to collect samples at 8 hours and 30 hours post-infusion, or only at 24 hours post-infusion. For FIX, samples were collected any time on days 2 and 3 post-infusion; the alternative would be to collect two samples on day 2 or

Table 1. Data extracted from chart review

DATA EXTRACTED FROM CHART REVIEW
Patient demographics: • Age • Weight • Height • Baseline factor level
PK estimates calculated by the WAPPS tool
Prophylaxis regimen before PK testing
Prophylaxis regimen after PK testing
Reason for changing the prophylaxis regimen (if available)
Reason for not changing the prophylaxis regimen (if available)

Table 2. Patient demographics

	PATIENTS WHO HAVE CHANGED THEIR PROPHYLAXIS REGIMEN AFTER PK TESTING	PATIENTS WHO HAVE NOT CHANGED THEIR PROPHYLAXIS REGIMEN AFTER PK TESTING
Age		
Mean ± SD	10.61 ± 4.16	9.89 ± 3.26
(Minimum, Maximum)	(2, 15)	(3, 15)
Weight (kg)		
Mean ± SD	45.72 ± 20.83	37.52 ± 14.53
(Minimum, Maximum)	(14, 76.9)	(14.5, 66.2)
Height (cm)		
Mean ± SD	149.12 ± 31.89	140.99 ± 20.75
(Minimum, Maximum)	(81, 184)	(95.8, 175)

3, optimally 4+ hours apart. Of note, the collection times were all indicative (i.e. 24 hours can be any time between 18 and 30 hours) and samples were collected based on timings that were feasible for patients since WAPPS is able to use sparse sampling to calculate PK data.

The study was approved by the Hamilton Integrated Research Ethics Board. Participants in the WAPPS database gave prior informed consent for data input in this database.

RESULTS

Overall, 31 patients were included in this study. All of those included had a baseline factor level of less than 0.01 IU/mL; 42% (n=13) changed their prophylaxis regimen after PK testing. Demographic information is presented in Table 2; Table 3 illustrates the specific changes to the prophylaxis regimen (e.g. dosage, frequency and/or drug).

Of the 13 patients who changed their prophylaxis regimen after PK testing, 62% (n=8) had their dosage increased and frequency decreased. Reasons for change in prophylaxis regimen included: potential for greater adherence to prescribed regimen (n=2), decreased bleeding episodes (n=3), increased blood factor levels (n=3), more consistent/easier to follow schedule (n=1), better fit for lifestyle (n=2), decreased frequency to mitigate venous access issues (n=1), and patient preference (n=1). One family mentioned that their quality of life improved significantly after changing their prophylaxis regimen. After using WAPPS to optimise the prophylaxis regimen, there was a decrease in the number of hours per week where factor level was under 1% (from an average of 13.1 hours/week to 11.8 hours/week), though not statistically significant (p=0.16, one-tailed) (Figure 1). Of note, due to unavailable data, these averages of time per week (and Figure 1) did not include one patient whose drug was changed after WAPPS.

Reasons for not changing the prophylaxis regimen after PK testing included: current regimen found to be appropriate (n=7), patient was stable without significant bleeding (n=3), and patient preference (n=1). There were seven patients who did not change their prophylaxis regimen after PK testing but for whom no specific reason was documented. The half-life estimates were not statistically significant between patients who changed their regimen after PK testing and those who did not (p=0.49, two-tailed).

Amongst the 31 patients included in the study, three had haemophilia B, and 28 had haemophilia A. Of the three haemophilia B patients, only one changed their

Table 3: Changes to prophylaxis regimen after WAPPS

CHANGES TO PROPHYLAXIS REGIMEN			
DOSAGE	FREQUENCY	DRUG	NUMBER OF PATIENTS (N)
↑	↓	—	8
↑	—	—	1
↓	—	—	1
↓	↑	—	1
—	↑	—	1
—	—	Changed	1

↑ indicates increase ↓ indicates decrease — indicates no change

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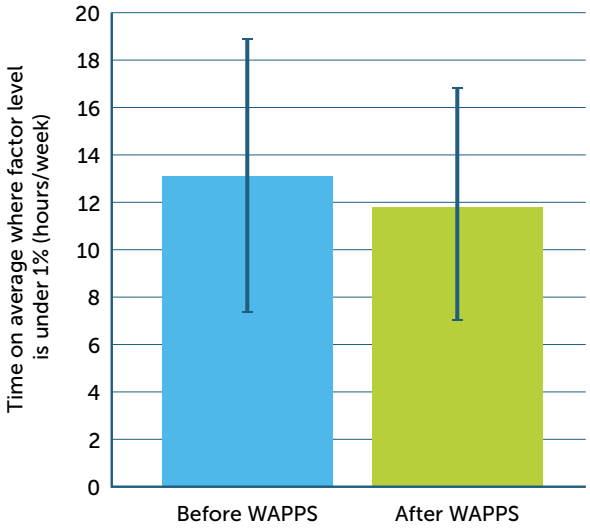
Figure 1. Change in hours per week where factor level is under 1% pre- and post-PK testing using WAPPS. Error bars represent the standard error.



regimen after PK testing to increase their trough levels. Two of the three haemophilia B patients did not change their regimen; one for no specific documented reason, and the other found that their current regimen was sufficient. The median half-life estimates for FIX and FVIII were 32 hours and 11.5 hours respectively. In all three haemophilia B patients there were zero hours per week where factor level was under 1% and this did not change after WAPPS. Amongst the haemophilia A patients, this changed from 14.5 hours before WAPPS to 13.1 hours after WAPPS.

DISCUSSION

Overall, our study shows that PK data generated by WAPPS has direct clinical impact by informing changes to prophylaxis recommendations. These results are in keeping with Nagao et al.'s study which examined the clinical impact of population-based PK tools, including WAPPS, in a sample of 39 participants with haemophilia A aged 2–67 (median age 19) [7]. This study revealed that 20 out of the 39 participants reconsidered their prophylaxis regimen after the population-based PK analysis; eight had their dosage increased, five decreased the interval of infusions between doses, five changed their coagulation factor from a standard half-life product to an extended half-life product, and two reduced their dosage [7]. Similarly, Croteau et al. conducted a multi-centre prospective feasibility study of PK-tailored prophylaxis regimens using WAPPS in 15 patients (adults and children) with haemophilia A [8]. This group found that 9 out of 15 patients did not change their prophylaxis regimen after WAPPS, but three patients increased the frequency of infusions and two decreased the frequency of infusions [8].

An important finding from our study is that WAPPS informs changes to prophylaxis regimens without increasing the time spent with factor levels below 1% and risking patient safety. This result is consistent with that from Nagao's group, which found a tendency towards decrease in bleeding rates, though not statistically significant, when dosing of the regimen (dosage, frequency) after population-PK analysis changes but the product stays the same [7]. Likewise, Valentino et al. published a randomised trial comparing standard and PK-tailored prophylaxis in a sample of 66 patients aged 7–59 years and found that the two prophylaxis regimens had no difference in annual bleeding rates and were similar in terms of safety [2]. Of note, some studies have found that PK-tailored prophylaxis was able to reduce the number of bleeds per year [9,10].

Another interesting finding from our study is that the majority of prophylaxis regimen changes after WAPPS involve increasing the dosage and decreasing the frequency (n=8). With fewer infusions, there may be a decreased need for central venous catheter (CVC) insertion, specifically in younger children in whom frequent venepuncture is difficult. This in turn may help to decrease CVC complications such as deep vein thrombosis and line-related sepsis [6]. Another advantage with fewer infusions is the potential for greater treatment adherence, especially in the paediatric population where compliance with long-term treatment can be difficult [2]. Although treatment adherence was not assessed in our study, Nagao et al.'s study found that adherence was improved in those with a shortened infusion interval after population-PK analysis, and in those who switched to an extended half-life product [7].

Of note, even amongst those who have not changed their prophylaxis regimen after PK testing, WAPPS can be helpful for confirming the appropriateness of the prescribed regimen. In this retrospective study, seven of the 18 patients who did not change their prophylaxis regimen were found to have an appropriate regimen (sufficient dosage, half-life, factor level) and this was the most common reason for not changing the regimen after PK testing. WAPPS can thus provide feedback to clinicians and to the community, not only with regards to optimisation and individualisation of treatment recommendations, but also to confirm and validate clinical practice. Furthermore, it can be used as an educational tool that fosters communication and discussion with patients even if they decide to not make changes to their regimen after PK testing. For instance, we have found that some patients prefer their current

regimen and do not want to change it after having a discussion with their care provider.

WAPPS also supports the practice of patient-centred care. In this study, many of the reasons for change (or no change) in prophylaxis regimen revolve around patient preference, values and needs. One family specifically mentioned that their quality of life improved significantly after tailoring their prophylaxis regimen. This individualised approach may further enhance patient engagement and adherence

Finally, this tailored prophylaxis approach may optimise cost-efficient factor usage. Although no cost-benefit analysis was conducted in the current study, investigating the cost-effectiveness of WAPPS would be of interest in future studies. It would also be of interest to repeat this study at other centres with a larger sample size, and a longitudinal study looking at the long-term impact of WAPPS-Hemo would be of value. PK estimates evolve throughout childhood alongside physiological changes in paediatric patients; for instance, metabolising enzymes mature and develop, affecting the half-life of certain drugs [11]. Given these evolving PK parameters in childhood, it would also be of interest in future studies to assess the optimal frequency of PK testing in paediatric haemophilia patients.

CONCLUSION

This study has demonstrated the impact of using PK data generated by WAPPS in paediatric patients with severe FVIII and FIX deficiency. By informing changes to prophylaxis recommendations using WAPPS, this patient-centred approach engaged patients without increasing the time spent with factor levels below 1%. In cases where PK testing did not result in a change to the prophylaxis regimen, the study also demonstrated that this approach could be helpful in confirming and validating clinical practice, and that it may serve as an educational tool that fosters communication with patients and families. Future studies to further evaluate the clinical benefit and cost-effectiveness of WAPPS would be of interest.

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Author contributions

CK and AC conceived and designed the study. MB, KD, KS, DM and AC provided mentorship, methodological and statistical support. CK completed the analysis and drafted the manuscript. All authors provided edits and contributed to the final version.

Consent

This article reports a retrospective study in which no human participants or animals are directly involved. Participants in the WAPPs database gave prior informed consent for data input in this database.

Disclosures

The authors have advised no interests that might be perceived as posing a conflict or bias.

ORCID

Celia Kwan https://orcid.org/0000-0003-1685-488X
Mihir D. Bhatt https://orcid.org/0000-0003-3233-4067
Karen Strike https://orcid.org/0000-0002-5598-2051
Kay Decker https://orcid.org/0000-0002-6847-3192
Davide Matino https://orcid.org/0000-0002-9902-4074
Anthony K.C. Chan https://orcid.org/0000-0003-1551-3995

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