MANIPULATION OF WARFARIN TABLETS IN PAEDIATRIC CARE:

Do we give the right dose?

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BACKGROUND

Manipulation of drug formulations to achieve an appropriate dose is often necessary in the pediatric ward (e.g crushing and dispersion of tablets, followed by extraction of a fraction). However, such manipulation has previously been shown to result in inaccurate dosing for some tablet formulations of the poorly soluble anticoagulant aspirin. Using the same manipulation procedure a dispersible tablet formulation of aspirin yielded 99% of the intended dose wile a chewable tablet yielded only 9% (Notaker, 2016). Warfarin is another anticoagulant used in paediatric care. Despite having good solubility ensuring a reliable dose of this substance is important, considering the narrow therapeutic index of the drug.

PURPOSE

- To investigate the dose accuracy and dose precision obtained after manipulation of two different warfarin tablets, using validated UHPLC-analysis (Ultra High Performance Liquid Chromatography)
- To compare the two warfarin tablets
- And compare the results for the two tablets with results found previously for an anticoagulant with different physical properties (aspirin).

MATERIALS AND METHODS

Warfarin tablets: *Marevan* (warfarin sodium, 2.5 mg), Takeda AS, Norway, and *Warfarin Orion* (warfarin sodium, 2.5 mg), Orion Pharma, Finland.

Method: *Instrument:* UHPLC-system from Shimadzu Corp (Nexera, with Prominence DAD-detector). Analytical column: Inertsil 2 µm C8-3, 2.1 x 100 mm, (GL Sciences Inc., Tokyo, Japan). Mobile phase: Methanol : Water : Acetic acid, 68:32:1 (V/V). The analytical method was validated for linearity, precision, and specificity.

THE MANIPULATION

Method: Six tablets from each of the two formulations were individually dissolved in 10 ml water. After 8 minutes, a sample (1 ml; one tenth of a tablet) was withdrawn from "Zone 2" (at 2 mL mark). Dosing accuracy and precision was recorded and compared between tablets.

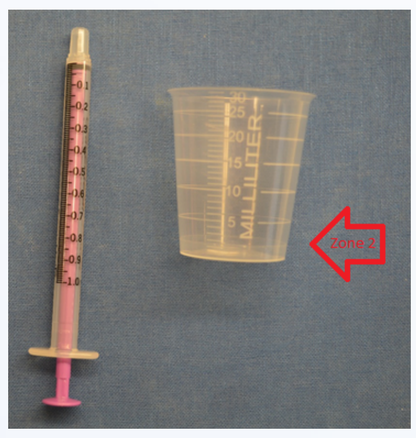

Figure 1: *Medicine measure (30 mL) and oral syringe (1 mL) used for manipulation.*

WARFARIN vs ASPIRIN

For the very soluble drug warfarin sodium two tablets both gave accurate doses upon manipulation (ie dispersion and extraction of a tenth of a tablet) (Figure 2).

The dosing accuracy of *Dispersible Aspirin* (75 mg) and *BayerChewable* (81 mg) upon manipulation has previously been presented (Notaker, 2016). The two different tablets containing this poorly soluble drug differed markedly in the dose accuracy delivered (Figure 2).

API	Solubility in water
Aspirin	1:300 (Merck Index 13th)
Warfarin sodium	«Very sol» (Merck Index 13th)

RESULTS

For *Warfarin Orion* (2,5 mg) 96.5 % (sd:4.8; range 89.8–101.4%; n=6) of the intended dose was found. For *Marevan* (2,5 mg) 101.4 % (sd: 4.2; range 96.3–107.2 %; n=6) of intended dose was found.

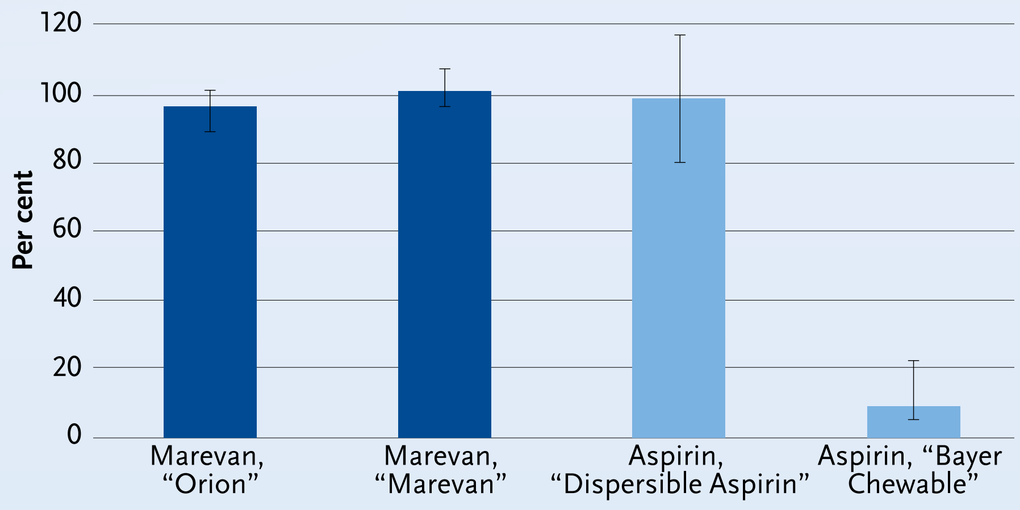

Figure 2: *Per cent of intended dose obtained after dispersing one tablet in 10 mL water and extracting 1 mL with a 1 mL syringe. Intended dose = 1/10 of the tablet. The accuracies obtained for the warfarin sodium tablets are compared to results obtained previously for Aspirin tables (Light blue columns; Notaker, 2016)*

CONCLUSIONS

Using a validated UHPLC-method the dosing accuracy upon dispersion and dose extraction from two warfarin tablets (*Marevan* and *Warfarin Orion*) was found to be both accurate and precise – unlike what has previously been published for different aspirin tablets. These results underlines the importance of considering API characteristics as well as formulation properties when manipulating tablets to obtain a fraction

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