CONCEPTS IN HYPERTENSION

A Journal Article-Based Approach to Understanding the Clinical Aspects of Hypertension

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Article of Interest

Grahnen A, et al. Implications of Intraindividual Variability in Bioavailability Studies of Furosemide. European Journal Clinical Pharmacology. 1984. (Click to Access)

Context and Study Objective

Because furosemide was introduced before the era of large-scale clinical trials, it was not subjected to the same level of scrutiny as contemporary therapies. As a result, its flaws are less publicized. In this paper by Grahnen, the bioavailability (fraction of the administered drug that enters the circulation and is biologically active) of oral furosemide was determined in order to guide dosing recommendations.

Design, Setting, and Participants

Four women and four men aged 25-27 and weighing between 53-82 kg participated. All were healthy and not on medication. No further background information was provided. In a randomized, blinded fashion, each received 40mg of either oral or IV furosemide on a weekly basis for 6 weeks. The drug was given after an overnight fast. The bioavailability of oral furosemide was computed by comparing its serum concentration to that of IV furosemide (*n.b.* therapies administered IV are 100% bioavailable).

Results

-Among all-comers, the average bioavailability of orally administered furosemide was 55%.
-From one participant to the next, the systemic level of PO furosemide varied by as much as a factor of 4. It ranged from 20 to 85%.

Clinical Perspective

Bioavailability of Oral Loop Diuretics

	Furosemide	Bumetanide	Torsemide
Range in Bioavailability	10-90 %	60-90 %	80-90 %

-Despite this study's poor methodology, its simplicity makes it suited to highlight a critical shortcoming of furosemide -- its variable bioavailability. The below scenarios highlight the clinical uncertainty this generates.
-If I prescribe a 40 mg tablet to an office patient, the "average" systemic level will be equivalent to 20 mg IV. However, because the bioavailability varies between 20-85%, 40 mg PO may be the bioequivalent of 8 mg IV (20% of oral dose) or 32 mg IV (80% of oral dose).
-If an inpatient with heart failure requires 40 mg IV furosemide, should she be transitioned to the standard 80 mg pill? Perhaps. But if her metabolism results in a bioavailability closer to 80%, the discharge dose should be 50 mg PO. Yet if her metabolism is closer to 20%, the appropriate oral dose is 200 mg.
-Should the above patient re-presents with dyspnea 2 weeks later, can this be ascribed to medication non-adherence? Or was the furosemide under-dosed as a result of low bioavailability?
-Table: Widely circulated data from Brater indicates why more recent loop diuretics such as bumetanide and torsemide are my preferred oral agents. The narrower the range in bioavailability, the more predictable the therapeutic response.
-Disclosures: I have no conflicts to declare.

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