13 *Bioequivalence in migraine: influence of migraine on pharmacokinetics and gastric emptying*

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Introduction

In an attempt to improve clinical drug development, one has become increasingly attentive to how the rate and extent of absorption of a compound can be influenced by pathophysiological processes and how this can affect drug efficacy. Whereas previously the term bioequivalence was exclusively used to imply that the rate and extent of absorption of two pharmaceutical compounds did not differ statistically, it is now often used to refer to the changes in the kinetic properties of a compound when administered under different circumstances.

Migraine is known to delay the absorption of orally administered drugs, which leads to postponed therapeutic responses and smaller response rates. As anti-migraine compounds are specifically intended to rapidly abort an acute attack, their pharmacokinetic properties, which are directly linked to their efficacy, should be evaluated early in the development of new compounds. An overview is provided of the existing literature illustrating the influence of migraine headache on the bioequivalence of acute antimigraine drugs.

Gastro-intestinal symptoms in Migraine

In a majority of patients, migraine attacks are associated with gastro-intestinal symptoms ranging from mild nausea, to severe vomiting, diarrhoea and even abdominal pain (1). Those symptoms are not only a hassle for patients, but it is obvious that vomiting might reduce the efficacy of orally administered drugs. Furthermore, even in the absence

of overt gastro-intestinal symptoms, orally ingested drugs might not be absorbed at the normal rate during a migraine attack. This is due to gastric stasis that accompanies migraine headache and which has been documented as early as the 1930s by radiological observations using barium meals taken during migraine attacks (2). The most likely explanation is that during a migraine headache disturbances of the autonomic nervous system result in relaxation in the gut with contraction of the pyloric and ileocaecal sphincter.

Recently, Aurora et al. demonstrated that gastric emptying was apparently delayed in migraine patients outside attacks, which would indicate that autonomic dysfunction is present in migraine patients both ictally and interictally (3). The method of the study was nevertheless criticised as the study was done in a subgroup of migraine patients where a visual trigger could induce an attack. Later the authors also conducted the study in 3 patients during a spontaneous migraine headache, yielding the same results (4). As those findings are in contrast with several earlier pharmacokinetic studies, further studies are needed to investigate autonomic changes in migraineurs and the implications of this on therapeutic interventions.

Delay of drug absorption in migraine

Volans et al. were the first to describe in a well conducted pharmacokinetic study that the rate of effervescent aspirin absorption was decreased during migraine (5). They also observed that the ‘poor absorbers’ were more likely to have received additional treatment. In a subsequent study they observed that when aspirin was given with a concomitant intramuscular injection of metoclopramide, absorption was not significantly different from absorption in headache-free migraine subjects (6). In addition, none of the migraine patients treated with the combination of intramuscular metoclopramide and aspirin needed additional treatment.

Tokola et al. later described that a migraine attack not only delays absorption of orally administered paracetamol but also decreases its

relative bioavailability (7). This is due to an increased “first pass” metabolism when paracetamol is delivered more slowly to the small intestine as a consequence of delayed gastric emptying. The sulphate conjugation of paracetamol in the liver becomes saturated in adults at the therapeutic dose, meaning that a high percentage of paracetamol escapes the first pass metabolism in the liver and reaches the systemic circulation. When paracetamol is absorbed more slowly during a migraine attack, sulphate conjugation does not become saturated and bioavailability of paracetamol decreases. This is a nice illustration of how even the bioavailability of an orally administered drug can be influenced during migraine.

Gastric stasis is also known to influence the absorption of orally administered triptans with possible delay in symptomatic relief (8, 9). Sumatriptan can be administered subcutaneously to by-pass poor oral bioavailability and the effect of delayed gastric emptying (10). As patients often resent subcutaneous injection for drug administration, intranasal administration can be an elegant alternative and is available in most countries (11). It should nevertheless be noted that a large portion of intranasally administered drugs or swallowed and subsequently absorbed in the gastro-intestinal tract.

These days, the pharmacokinetic properties of novel anti-migraine drugs are assessed both during and outside of an acute migraine headache early in their clinical development (12, 13). This is crucial as the early absorption of an acute anti-migraine compound governs the likelihood of response (14).

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