

Why pharmacokinetic differences among oral triptans have little clinical importance: a comment

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Abstract Triptans, selective 5-HT_{1B/1D} receptor agonists, are specific drugs for the acute treatment of migraine that have the same mechanism of action. Here, it is discussed why the differences among kinetic parameters of oral triptans have proved not to be very important in clinical practice. There are three main reasons: (1) the differences among the kinetic parameters of oral triptans are smaller than what appears from their average values; (2) there is a large inter-subject, gender-dependent, and intra-subject (outside/during the attack) variability of kinetic parameters related to the rate and extent of absorption, i.e., those which are considered as critical for the response; (3) no dose-concentration-response curves have been defined and it is, therefore, impossible both to compare the kinetics of triptans, and to verify the objective importance of kinetic differences; (4) the importance of kinetic differences is outweighed by non-kinetic factors of variability of response to triptans. If no oral formulations are found that can allow more predictable pharmacokinetics, the same problems will probably also arise with new classes of drugs for the acute treatment of migraine.

Keywords Acute treatment · Disposition · Headache · Pharmacokinetics · Triptan · Variability

Introduction

The availability of many drugs for the management of a disorder should allow optimising the therapy, obtaining for individual patient maximum benefits with minimal side effects [1]. Triptans, selective agonists at 5-hydroxytryptamine 1B/1D receptor subtype, are among the few specific drugs which are effective and safe for acute migraine treatment [2]. Migraine is a very common disorder. Its lifetime incidence is 18% in men and 43% in women [3]. Although migraine is not life-threatening, it often heavily affects work and social functioning and reduces the overall quality of life [4].

The triptans are recommended as first-line drugs for patients suffering from moderate to severe migraine, associated with disability, who do not respond to COX-inhibitors [2]. Sumatriptan was the first to be marketed, at the beginning of the 1990s. Even if it is fast absorbed orally, its bioavailability is only 14% and it has a short half-life of about 2 h. Six other triptans have been later introduced: zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, and frovatriptan, which have greater oral bioavailability, longer plasma half-life, active metabolites, higher lipophilicity, and greater potency and affinity for 5-HT_{1B/1D} receptors [5]. Triptans are homogeneous in their mechanism of action [6]. It has, therefore, been thought that the differences with respect to their pharmacokinetics can cause a different efficacy, frequency of recurrence, and consistency of response, and they can therefore allow choosing the most appropriate triptan for each patient [7]. However, only minor differences in the efficacy of oral triptans for migraine have been

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Table 1 Some pharmacokinetic parameters of oral triptans

Triptan	C_{\max} (ng/ml)	AUC (ng h/ml)	T_{\max} (h)
Almotriptan 12.5 mg [22, 54]	49.5 ^a (13.5)	266.1 ^a (39.1)	2.5 ^a (0.7)
Eletriptan 20 mg [57]	61.5 ^b (32.5–116.5)	317.3 ^b (152.9–658.1)	1.0 ^c (0.5–1.5)
Frovatriptan 2.5 mg [58]	4.2 ^b M (3.19–5.61) 7.0 ^b F (6.02–8.14)	42.9 ^b M (36.3–50.7) 65.8 ^b F (65.8–134.3)	2.3 ^c M (2.0–2.5) 3.0 ^c F (2.0–4.0)
Naratriptan 5 mg [19, 59]	10.8 ^d M (7.1–14.2) 16.6 ^d F (9.8–37.3)	108.2 ^d M (76.6–168.1) 163.6 ^d F (89.9–256.5)	3.0 ^c M (2.0–6.0) 3.0 ^c F (1.0–6.0)
Rizatriptan 10 mg [20, 60, 61]	28.6 ^a M (13.5) 32.1 ^a F (11.9)	72 ^a (22) 97 ^a (28)	1.0 ^a (0.5) (range: 0.6–2.4) 1.2 ^a (1.0) (range: 0.4–2.0)
Sumatriptan 50 mg [31]	30.1 ^a (12.5)	103 ^a (49)	0.83 ^c (0.33–3.00)
Sumatriptan 100 mg [33]	53.2 ^a (29)	199 ^a (105)	1.0 ^c (0.5–4.00)
Zolmitriptan 2.5 mg [18]	3.0 ^a (1.7) 3.3 ^c M 3.8 ^c F	17 ^a (8.1) 17.7 ^c M 21.3 ^c F	2.0 ^c (0.5–6.0)

M males, F Females

^a Arithmetic mean (\pm SD)

^b Geometric mean (95% CI)

^c Median (range)

^d Arithmetic mean (range)

^e Geometric mean (range)

reported [5, 8]. In particular, the maximum response after oral administration, measured as pain relief after 2 h, is approximately 70% in clinical trials [9], and up to 40% of attacks fail to respond to a particular drug [10]. Furthermore, less than 2/3 of patients respond to a triptan in three out of three attacks [11]. Recurrence is a common event; in triptan trials, recurrence rates vary from 7 to 57% [12], and in patients using triptans headache return is associated to 24% of headaches which have had a pain-free response [13]. Indeed, 40–50% of patients report dissatisfaction with at least one aspect of their current triptan therapy [14], there is a marked variation in the individual patient response and preference for the available oral triptans [15, 16], and it seems that there are no characteristics which can make the difference between one drug and another [17]. Moreover, there is no clear method of choosing an appropriate oral triptan for a particular patient and, currently, this is achieved by trial and error [11].

Omitting pharmacodynamic aspects and the variability of response depending on metabolism, we have analysed here why pharmacokinetic differences among the various oral triptans have such a limited clinical importance.

Because of the interindividual variability of kinetic parameters

The differences among the kinetic parameters of the various triptans are less important than what can appear from

average values (arithmetic mean, median or geometric mean) of these parameters (Table 1). There is great inter-individual variability of kinetic parameters, which only emerges if, besides the average value, the standard deviation (i.e., the spread of data around the expected value), and the range of the values are also indicated. The interindividual variability is even more evident, if the coefficient of variation (CV, allowing comparison of data sets with different unit measures) or the confidence interval (CI, i.e., an interval likely to include as a parameter) is expressed. This variability reduces the difference between a drug and another, makes the comparison among triptans difficult, and limits the possibility to predict with a good chance of success the kinetics of a certain triptan in an individual patient.

Numerous kinetic parameters of triptans vary, also in a statistically significant way, according to gender (Table 2). In particular, C_{\max} (the peak plasma concentration) and $AUC_{0-\infty}$ (the area under plasma concentrations from 0 to infinity) of frovatriptan, naratriptan, rizatriptan, and zolmitriptan are significantly lower in males than in females. These differences have been partially attributed to higher bioavailability in females and higher total body clearance in males [18–22]. Kinetic variations according to gender have generally received little attention from researchers also because, according to producers, no dose adjustment is needed depending on the patient's gender. This statement makes it clear the limited importance of plasma concentrations, in particular of maximum ones, as a parameter by itself, indicative of the response [23]. It also

Table 2 Male/female ratio of the pharmacokinetic parameters of some oral triptans

Triptan	Male/female ratio of pharmacokinetic parameters						
	Bioavailability %	C_{\max} (ng/ml)	AUC _{0-∞} (ng h/ml)	T_{\max} (h)	Vd (L)	$t_{1/2}$ (h)	CLp (ml/min)
Almotriptan 12.5 mg [22]	NS	NS	NS	NS	–	NS	NS
Frovatriptan 2.5 mg [21]	0.88	0.60	0.46 ^a	0.66–0.77	1.66	1.07	1.64
Naratriptan 5 mg [19, 59]	0.85	0.79	0.66	–	–	–	1.25
Rizatriptan 5 mg [20, 60, 61]	–	0.96	0.78	0.77	1.31	0.92	1.27
Rizatriptan 10 mg [20, 60, 61]	–	0.89	0.74	1.00	1.38	0.92	1.22
Zolmitriptan 2.5 mg [18]	1.00 ^b	0.87 ^c	0.83 ^d	1.54	1.04	0.90	1.13
Zolmitriptan 5 mg [18]	0.78	0.62	0.56	–	–	0.92	–

NS no statistically significant differences, – datum not available

^a AUC₀₋₁₂ = 0.63

^b 95% CI = 0.84–1.26

^c 95% CI = 0.60–1.05

^d 95% CI = 0.61–1.09

suggests that the differences in the mean values of the pharmacokinetic parameters of triptans cannot predict a different efficacy.

Because the dose-concentration–response relationship is not definite for oral triptans

Pharmacokinetic factors will influence the disposition of a drug in the body, and ultimately, the concentration of unbound, or free, drug at the receptors, fundamental to the drug's effect. For pharmacokinetic factors to be of relevance, alterations in the concentration of drug at the receptor must cause changes in the amount of the drug effect. In other words, a dose-concentration–response relationship must be discernible. Most pharmacokinetic studies have been unfortunately carried out in healthy volunteers or migraine patients, but outside the attack. Furthermore, the responses to the triptan in migraine attack treatment are time-dependent [24, 25]. All triptans are more effective, if they are taken early and when pain is mild [26]. Also for these reasons, plasma concentrations are not directly related to the effect and the clinical response, and the dose-concentration–response curve has not been defined for any oral triptan [25, 27, 28]. Therefore, it is impossible to compare triptans and objectively verify the importance of the differences in pharmacokinetic parameters during the migraine attack.

Because few pharmacokinetic parameters can be used to compare triptans

The changes in the plasma concentrations of the triptan in the initial phase (till 2 h after administering the drug) have

been considered important to relate kinetics to clinical response. This phase is characterised by the extent and rate of absorption. However, the initial rate of absorption seems to be related to the patient's response more than the height of the plasma concentrations reached [28–30]. The key variable is therefore T_{\max} (time to peak concentration), which indicates the rate of absorption [31]. Nevertheless, this parameter is the one which presents the highest inter-individual variability. The comparison between T_{\max} and therapeutic gain at 2 h after administering different formulations of sumatriptan (oral, rectal, intranasal, subcutaneous, and intravenous) shows the importance of this parameter. An inverse relationship has been observed between T_{\max} and therapeutic gain: the fewer T_{\max} , the higher therapeutic gain after 2 h [32].

C_{\max} , AUC₀₋₂, C_{\max}/T_{\max} , AUC_{0-2}/AUC_{0-t}, AUC_{0-∞}/ T_{\max} , and $C_{\max}/AUC_{0-∞}$ have also been proposed to assess the rate and extent of absorption [29, 33, 34]. However, these parameters can only be used to compare different formulations of the same triptan, and not different triptans, since data about the time-course of plasma concentrations in connection with the dose and response are missing, and we do not know the minimum effective concentrations of oral triptans which have different potency.}}

Because of the variability of oral absorption

An oral drug should allow, besides easy taking, an effective, fast, and predictable absorption, in order to assure a response in most subjects. In the case of triptans, with the same oral dose, plasma concentrations vary a lot from one patient to another, especially in the first phase after oral administration, i.e., the most critic one for response [35]. For example, after the administration of oral sumatriptan

200 mg, maximum plasma concentrations varied from 52 to 227 ng/ml in healthy volunteers [34]. Plasma levels after administering oral zolmitriptan 10 mg in migraine patients outside the attack varied from 3 to 27 ng/ml after 2 h [36]. In addition, multiple peaks in plasma concentrations are found in some individuals after oral administration of sumatriptan, rizatriptan, and zolmitriptan [18, 30, 37]. The mechanism of this phenomenon has not been explained. It could be due to the different rates of stomach emptying or intestinal transit [38]. After oral administration of zolmitriptan, the time to achieve C_{\max} varied from 0.5 to 6 h, since some subjects had multiple peaks [36]. One of the factors which influence absorption is also the rate of stomach emptying, which is a unique characteristic of each individual [39]. Migraineurs have delayed gastric emptying during and between migraine attacks [40]. The variability of absorption is very likely to increase even more during the migraine attack when there is gastric stasis [41]. The absorption of any triptan during the attack can therefore be unforeseeable and erratic, and the outcome is not consistent [28, 42, 43]. During the migraine attack (Table 3), the amount absorbed and the plasma maximum concentration decrease and T_{\max} increases. These changes in pharmacokinetic parameters are statistically significant or close to significance for some triptans. Since, in order to have a complete response, it is fundamental to achieve sufficient plasma levels of triptan quickly following the onset of pain, the impairment of drug absorption may be the cause of the therapeutic failure of an oral triptan. Indeed, when studying the pharmacokinetics of sumatriptan following 100 mg oral

dosage, it has been noticed that 10 migraine patients with satisfactory response to sumatriptan absorbed the drug significantly faster and achieved significantly higher plasma levels than patients with unsatisfactory response to oral sumatriptan [44].

The importance of an efficient absorption for the response is also evident if we consider that prokinetic agents may not only be used to eliminate nausea and vomiting, but also to promote absorption [45]. Among migraine patients who had not got adequate relief from triptans, 63% responded to oral sumatriptan 50 mg combined with metoclopramide 10 mg, while only 31% responded to sumatriptan administered alone [46]. In a small sample size trial, the combination of rizatriptan and trimebutine (another prokinetic agent) was also more effective than rizatriptan alone [47].

Differences in plasma half-life and recurrence

It is very plausible to assume that the rate of headache recurrence following treatments may be influenced by kinetic properties [48]. On this basis, it has been thought that a longer half-life causes a lower probability of recurrence [49]. Plasma half-life (the time it takes for the blood plasma concentration of a substance to halve) is certainly a parameter which can influence the duration of the action of a drug. In spite of this, plasma half-life can be different from biological half-life (the time it takes to halve pharmacologic activity) due to factors such as tissue accumulation, active metabolites, and strength of receptor interactions. Furthermore, a long plasma half-life can be clinically significant if it assures concentrations which stay for more time within the therapeutic range [48]. Without this information, half-life alone cannot be considered as an indicator of the frequency of recurrence. Frovatriptan, as all triptans, has multiexponential kinetics, but it is the one with the longest half-life (approximately 25–26 h if calculated in the final phase, up to 48–72 h after administration) [21]. This drug is also considered one of the triptans with lower frequency of recurrence calculated from 4 h on [49]. Frovatriptan is distributed in RBCs for 60% with a link described as reversible and time-dependent [21]. Nevertheless, its concentrations have been determined in whole blood, and the concentrations of the free drug, not bound to RBCs, have not been proved to be clinically effective. In a new analysis of data from previously published studies, it is reported that there were no significant differences in the frequency of relapse within 24 h after response at 4 h, between frovatriptan 2.5 mg and sumatriptan 100 mg, which has a half-life of only 2 h [50].

In any case, it is not completely clear which triptan is associated to a lower frequency of recurrence. The

Table 3 During/outside migraine attacks ratio of the pharmacokinetic parameters of some oral triptans

Triptan	During/outside migraine attacks ratio of pharmacokinetic parameters		
	C_{\max} (ng/ml)	$AUC_{0-\infty}$ (ng h/ml)	T_{\max} (h)
Almotriptan 12.5 mg ^a [22, 54]	0.93	1.00	1.23
Eletriptan 40 mg ^b [57, 62]	0.69 ^c	0.71 ^d	2.15 ^e
Frovatriptan 2.5 mg [58]	0.93 M 0.91 F	0.53	0.66
Naratriptan 5 mg [63, 64]	ND	ND	1.75–2.33
Sumatriptan 100 mg [65, 66]	0.80 ^f	–	–
Zolmitriptan 2.5 mg [18, 36]	0.75	0.56	1.6

ND no difference observed, – datum not available

^a No statistically significant differences

^b Statistically significant differences

^c CV = 90.2% during attacks

^d AUC_{0-8} , CV = 93.8% during attacks

^e CV = 77.2% during attacks

^f Bioavailability

comparison among different studies is not possible, for an endless number of methodological problems (e.g., differences in the study design, the populations used, the characteristics of the attacks, the doses administered, the definition of recurrence, relapse or return, the methods of registration of recurrence, and the presence of recurrence also after the administration of placebo) [12, 49, 51]. Consequently, any result can be interpreted for or against any medication.

Differences in bioavailability and consistency of response

Bioavailability describes the fraction of an administered dose of unchanged drug that reaches the systemic circulation and it is one of the principal pharmacokinetic properties of drugs. It has been stressed that this parameter has a direct relationship with the inpatient consistency of response of individual triptans [11, 17, 52]. For sumatriptan, which has an oral bioavailability of only 14%, the consistency of pain relief in two out of three attacks is 64% and in three out of three attacks, 33% [53]. For almotriptan, which has instead a higher bioavailability (70%), pain relief in two out of three attacks is 75% and in three out of three attacks, 50% [54]. However, even if rizatriptan has a

bioavailability of 40% (lower than almotriptan), it has a higher consistency of response, since pain relief in two out of three attacks is 86% and in three out of three attacks, 60% [55, 56]. Average bioavailability alone does not, therefore, indicate the consistency of response of a specific triptan.

It must be considered that when a medication is administered intravenously, its bioavailability is 100% and it does not practically vary from a subject to another. When a medication is instead administered via other routes (such as orally), its bioavailability is always lower and it may vary from patient to patient, for different factors such as gastric emptying rate, enzyme induction/inhibition by other drugs/foods, individual variation in metabolic enzymes, disease state affecting liver metabolism or gastrointestinal function. The presence of all these variables does not allow us to establish and foresee in clinical practice an eventual direct relationship between bioavailability and consistency.

Conclusions

The changes in kinetic characteristics are not always associated to detectable changes in the relationship between exposition and response to a drug. In the case of

Table 4 Non-pharmacokinetic factors of variability of response to triptans

Factors	Description
Dynamic variability	Dynamic variability can be studied in isolated tissues. In this case, a considerable variability in the response to triptans is also observed. For example, EC ₅₀ varies 51 times for the vasoconstrictive effect of sumatriptan on human cerebral arteries, 21 times for the effect of rizatriptan, and 69 times for the effect of eletriptan [67]
Variability of the mechanisms implicated in the migraine attack	During the migraine attack various mechanisms are activated. For example, only attacks associated with elevated salivary CGRP levels respond to rizatriptan. This could explain why some patients or attacks are non-triptan responders [68]
Genetic variability-polymorphisms	STin2 VNTR polymorphism of serotonin transporter gene could be an important genetic factor to confer a higher risk of inconsistent response to triptans in migraine patients [69]
Mechanisms of receptor adaptation	When an excess of mediator is present in the biophase, a process of desensitisation is activated, which makes receptors refractory. This phenomenon can explain why a second tablet of sumatriptan at 2 h does not increase initial efficacy and does not prevent or delay headache recurrence [70]
Selection of the patient	The patient must be capable to respond to the drug if we want a response. If the patient takes the triptan for a tension-type headache, the response is improbable, since triptans are not effective in episodic tension-type headache [71]
Placebo effect	In clinical practice, a patient's response to an active drug makes us wonder if this patient responds well because of the medication (and its kinetic properties) or because of the placebo effect (caused, for example, by the patient's positive expectations and by the physician who has prescribed the drug) [72]
Fluctuation of migraine	The course of migraine can vary in years: changes in this disorder are likely to influence the response to triptans [73]
Prophylactic treatments	The use of prophylactic medications increases the consistency of response to triptans [10, 24]
Previous therapies	In individuals with migraine, recent prior opioid use reduces triptan response [74]
Time of medication administration and severity of the migraine attack	The response to triptans is higher and more complete if they are taken early, and when the pain is of mild intensity [26]

migraine, with oral (and maybe also nasal and rectal) triptans, the importance of kinetic differences is already low for the large variability observed (intersubjects, intrasubjects, gender-related, in healthy volunteers, and in migraine patients outside and during the attack). Furthermore, it is outweighed by the number and importance of non-kinetic sources of variability (Table 4). Choosing an oral triptan according to a mean pharmacokinetic parameter is not an efficient method, since it does not allow choosing, with good probabilities of success, the most appropriate triptan for each patient or to predict which patient will respond to which drug.

Pharmacokinetic parameters are fundamental for the efficacy of a drug, since they influence the arrival at the site of action with the fit concentration. Nevertheless, if their variation range is very large, the behaviour of a certain drug becomes unforeseeable in that specific case. This is why the physician must know the pharmacokinetics of each triptan, but (since he will never have to treat the average patient) also how and why kinetic parameters and the response to the drug can vary in the patient. As a conclusion, understanding variability means understanding the complex relationships among physiology, pathology, pharmacology, and clinical response.

If no new formulations are found allowing more predictable pharmacokinetics, similar problems are very likely to be present also with new classes of drugs. It should, therefore, be useful to become familiar with these issues. The physician's ability to manage uncertainty and unforeseeable aspects of therapy can strongly influence the relationship with the patient and, consequently, the long-term results of migraine treatment.

Conflict of interest None.

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