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REVIEW

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Parenteral vs. oral sumatriptan and naratriptan: plasma levels and efficacy in migraine. A comment

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Abstract The clinical efficacy in migraine was compared for oral and subcutaneous sumatriptan and naratriptan. Doses of the two administration forms were chosen as resulting in comparable blood concentrations. Subcutaneous administrations of the drugs were superior for efficacy than the oral forms. This most likely due to a quicker rise in blood concentrations after subcutaneous injections.. In designing new therapies for migraine one should aim at a quick absorption of the drug, which will probably result in an increased efficacy.

Keywords Migraine • Sumatriptan • Naratriptan • Oral administration • Subcutaneous administration

Introduction

The pharmacokinetic/pharmacodynamic relationship for triptans in migraine has rarely been investigated [1–3]. In one study patients were selected as non-responders, responders and patients with headache recurrence and the pharmacokinetic parameters for sumatriptan outside attacks were compared [3]. No differences were found [3]. In addition, the effect of sumatriptan on the common carotid artery and its branches was quite comparable among the groups [3]. Ideally, one should use simultaneous measurements of plasma levels of the drug and pharmacodynamics, in this case the headache response. This approach has only been used in one small pharmacokinetic study in which 11 of 20 patients responded to oral zolmitriptan [1]. The plasma concentrations of zolmitriptan were generally higher in responders than in non-responders [1].

In a meta-analysis subcutaneous sumatriptan was superior to oral sumatriptan [4, 5] and it has been suggested that the higher efficacy rate for subcutaneous sumatriptan is dependent on a quicker speed of absorption [6, 7]. The present comment is an attempt to explore this point further.

Methods and results

Pharmacokinetic data for sumatriptan and naratriptan were taken from studies in healthy volunteers in the literature [4, 5, 8] and for subcutaneous naratriptan from a study in migraine patients [9]. These pharmacokinetic data were compared with the efficacy of subcutaneous and oral sumatriptan and naratriptan in randomised clinical trials [6, 9, 10].

Doses for comparison of subcutaneous and oral drugs were selected as those resulting in roughly similar maximum plasma levels (C_{max}). For the chosen doses of sumatriptan (subcutaneous 6 mg and oral 300 mg) and naratriptan (subcutaneous 1 mg and oral 2.5 mg) the C_{max}, time to maximum concentration (T_{max}) and therapeutic gain (TG) (percentage response after active drug minus percentage response after placebo) are shown in Table 1.

The oral bioavailability for sumatriptan is 14% [8], which is substantially lower than its subcutaneous bioavailability of 96% [8]. The oral bioavailability is decreased further by 20% during migraine attacks [8]. The C_{max} for subcutaneous sumatriptan 6 mg is 72 ng/ml, whereas the C_{max} is 112 ng/ml for oral sumatriptan 300 mg [8]. For subcutaneous sumatriptan 6 mg the TG for headache relief (a decrease from moderate or severe headache to none or mild) [11] is 51% after 1 h [8]. After 2 h the headache relief increases to 81%–87% but the TG for subcutaneous sumatriptan remains the same (50%) because the placebo response increases correspondingly [6]. For oral sumatriptan 300 mg the TG for headache relief is 40% after 2 h [12]. The T_{max} is 10 min for subcutaneous sumatriptan 6 mg [4] and the T_{max} is 3 h for oral sumatriptan 300 mg [8].

The oral bioavailability of naratriptan is 74% [4] and there is a virtually complete subcutaneous bioavailability [9]. For naratriptan pain-free responses at 2 h, the currently suggested primary efficacy measure [11] is available. The TG for pain-free is only 16% for oral naratriptan 2.5 mg [10] and it is 27% for subcutaneous naratriptan 1 mg [9]. The C_{max} is 13 ng/ml for oral naratriptan 2.5 mg [8] and the C_{max} is 16 ng/ml for subcutaneous 1 mg [9]. The T_{max} is 10–20 min for subcutaneous naratriptan [9] and the T_{max} for oral naratriptan is 2 h [4].

Comments

Thus, for both triptans in doses resulting in roughly similar maximum plasma levels after subcutaneous and oral administrations (Table 1) one gets a higher headache response with the subcutaneous formulation.

A prerequisite for considering the pharmacokinetic/pharmacodynamic relationship is an established dose-response curve. There are dose-response curves for both subcutaneous sumatriptan (1–8 mg) [4, 13, 14] and subcutaneous naratriptan (0.5–10 mg) [9]. For oral naratriptan there is a dose-response curve from 0.1 to 10 mg, with 1 mg being the minimum effective dose [15–17]. However, the dose-response curve for oral sumatriptan is poorly defined. Sumatriptan 100 mg (60%–67%) is not different from 200 mg (73%) and 300 mg (71%) [12]. This could be due to a ceiling effect for oral sumatriptan. That a ceiling effect is not inherent to triptans *per se* is illustrated by the fact that the highest subcutaneous dose, naratriptan 10 mg, resulted in 88% pain-free after 2 h [9, 18]. The badly defined dose-response curve for oral sumatriptan makes the comparison of subcutaneous and oral sumatriptan somewhat difficult and the results for sumatriptan should therefore be judged with some reservation.

Another confounding factor is the possible influence of the migraine attack with gastric stasis resulting in delayed oral absorption of drugs [19, 20]. The oral bioavailability of sumatriptan is thus 20% lower during migraine attacks [8] and the C_{max} for sumatriptan 300 mg is probably reduced to a similar extent during a migraine attack. For oral naratriptan the T_{max} increases from 2 h to 3.5 h during a migraine attack [21].

Both sumatriptan and naratriptan in the subcutaneous administration form were apparently superior to the oral form of the drugs (Table 1). It has been suggested that the mechanism of headache relief could be correlated to the rate of initial rise of plasma levels (T_{max}), to the height of the plasma levels (C_{max}) or the amount of the drug absorbed, area under the curve (AUC) [2]. The AUCs in the chosen doses are smaller for subcutaneous than for the oral forms of sumatriptan [6, 8] and naratriptan [6, 8, 9], so the total amount of

Table 1 T_{max}, C_{max} and therapeutic gain[a] for subcutaneous (s.c.) and oral sumatriptan and naratriptan (for choice of doses, see text)

	Sumatriptan		Naratriptan	
	6 mg s.c.	300 mg oral	1 mg s.c.	2.5 mg oral
T_{max} (min)	10	180	10–20	120[b]
C_{max} (ng/ml)	72	112[c]	16	13
	Headache relief	Pain-free		
Therapeutic gain	51%[d]	40%[e]	27%[e]	16%[e]

[a]: percentage response after active drug minus percentage response after placebo; [b]: increases to 3.5 h during migraine attacks [21]; [c]: probably 20% lower during migraine attacks [7]; [d]: after 1 h; [e]: after 2 h

drug absorbed cannot explain the difference. The C_{max} values were roughly equivalent (Table 1). Therefore, the most likely explanation for the differences in efficacy is the rapid initial rise in plasma levels, which is reflected in a shorter T_{max} (Table 1), after subcutaneous administration.

How earlier exposure to drugs results in a higher response remains an enigma. Investigations on blood vessels *in vitro* could elucidate whether similar responses occur in isolated cranial arteries. If present there are possibilities to study this further with pharmacological investigations at the receptor level.

From a clinical point of view subcutaneous administration is optimal when a really quick effect is needed. Thus the quick absorption of subcutaneous sumatriptan 6 mg results in a clinically relevant TG for headache relief of 22% already after 20 min in migraine [5]. It is also very effective in short-lasting but very severe cluster headache attacks, with a TG of 48% within 15 min [22].

Subcutaneous naratriptan 10 mg was superior to subcutaneous sumatriptan 6 mg for pain-free: difference=+33% (95% confidence intervals: +15% to +51%) [9, 18]. This may be due to the higher potency of naratriptan. Thus the pK_i for inhibition of radioactive ligand binding for 5-HT_{1B} is 8.1–8.7 for naratriptan and 7.8 for sumatriptan [4]. In addition, naratriptan is 2–3-fold more potent than sumatriptan in some animal models relevant for migraine [23]. Subcutaneous naratriptan was, however, not developed further for subcutaneous use but was developed in a low oral dose of 2.5 mg causing no more adverse events than placebo [10, 18].

Even if subcutaneous injections are more effective than tablets, most patients prefer to use tablets and the high price for subcutaneous sumatriptan (€35 per injection in Denmark) is also prohibitive in many cases.

In conclusion, the subcutaneous route of administration of a triptan is superior to the oral route. This is most likely due to the rapid initial rise in blood levels after the subcutaneous injection. In designing new therapies for migraine one should aim at a quick absorption of the drug, which will probably result in an increased efficacy.

Conflicts of interest: Peer Tfelt-Hansen has consulted for or conducted studies for AlmirallProdesfarma, Johnson & Johnson, Pfizer, Pozen Inc., and Vanguard.

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