**Pharmacokinetics of sumatriptan in non-respondent and in adverse drug reaction reporting migraine patients**

**Abstract** Sumatriptan is a selective agonist of 5HT1 (1B/1D) receptors, which has proved to be effective and safe for the acute treatment of migraine attacks. Nevertheless, its use by migraine sufferers is still limited and some patients consider adverse reactions related to sumatriptan, especially chest symptoms, unacceptable even if not serious. Moreover, in clinical trials, almost one third and one sixth of patients, respectively, fail to experience headache relief either after oral or after subcutaneous sumatriptan administration. Our aim was to verify whether differences in sumatriptan pharmacokinetics could explain non-response and/or adverse drug reactions. Sumatriptan levels were determined by HPLC with electrochemical detection. Pharmacokinetic parameters were calculated using a computer program (PK Solutions 2.0; non compartmental Pharmacokinetics Data Analysis). After oral administration, sumatriptan is rapidly absorbed and sometimes displays multiple peaks of plasma concentration. This “multiple peaking” gives rise to considerable inter-subject variability in the time of reaching maximum plasma concentration. Pharmacokinetic parameters of sumatriptan, both after oral and subcutaneous administration, were similar in the three patient groups. Blood pressure and heart rate did not show any significant differences between groups. Pharmacokinetic parameters and bioavailability of sumatriptan did not seem to be correlated either to the lack of efficacy or the appearance of side effects. These results could depend on the limited number of patients studied.

**Key words** Sumatriptan • Pharmacokinetics • Non-respondent patients • Reporting adverse-effects patients

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**Introduction**

Sumatriptan is a selective agonist at vascular 5-hydroxytryptamine 1B/1D receptor subtypes with high affinity and relative specificity for the 5-HT1D receptor subtype. Sumatriptan is rapidly absorbed after oral administration, with 80% of the maximum plasma concentration ($C_{\text{max}}$) occurring 45 min after administration of a single 100 mg dose, and a median $C_{\text{max}}$ of 49 ng/ml. Time to $C_{\text{max}}$ ranges from 0.5 to 3–4 h [1].

Sumatriptan is very rapidly absorbed into the systemic circulation following subcutaneous dosing; in fasting subjects peak plasma concentration occurs within 20 min. The
extent of absorption of sumatriptan by the subcutaneous route is 96%–97%, whereas it is much lower by the oral route. This lower bioavailability following oral administration is mainly the result of pre-systemic metabolism in the gut wall and in the liver, and consequently the inter-subject variability in plasma concentrations is much greater following oral dosing than after parenteral administration [2].

Sumatriptan has proved to be effective and safe for the acute treatment of migraine attacks [3]. Nevertheless, its use by migraine sufferers is still limited, and some patients consider adverse reactions related to sumatriptan, especially chest symptoms, unacceptable, even if not serious [4]. Moreover, in clinical trials, almost one third and especially chest symptoms, unacceptable, even if not serious [4]. Moreover, in clinical trials, almost one third and especially chest symptoms, unacceptable, even if not serious [4]. Moreover, in clinical trials, almost one third and especially chest symptoms, unacceptable, even if not serious [4]. Moreover, in clinical trials, almost one third and especially chest symptoms, unacceptable, even if not serious [4]. Moreover, in clinical trials, almost one third and especially chest symptoms, unacceptable, even if not serious [4]. Moreover, in clinical trials, almost one third and especially chest symptoms, unacceptable, even if not serious [4]. Moreover, in clinical trials, almost one third and especially chest symptoms, unacceptable, even if not serious [4]. Moreover, in clinical trials, almost one third and especially chest symptoms, unacceptable, even if not serious [4]. Moreover, in clinical trials, almost one third and especially chest symptoms, unacceptable, even if not serious [4].

So far, we determined sumatriptan pharmacokinetics in the following migraine patients: group 1, 3 females (mean age±SD: 51.5±12.0 years), who obtained headache relief; group 2, 3 males (mean age±SD: 49.0±1.4 years), who were non-responders; group 3, 3 females (mean age±SD: 37.0±1.2 years) who reported unacceptable adverse drug reactions. Each subject was studied twice, after oral and after subcutaneous administration of sumatriptan. A 1-week washout period was allowed between the administration of the two formulations. Patients were studied outside migraine attacks.

Blood samples were taken at baseline, at 15 and 30 min and at 1, 2, 3, 4, 5 and 6 h after sumatriptan oral administration, and at baseline and at 2, 5, 10, 15, 20, 25, 30, 60, 90, 120, and 180 min after subcutaneous injection. Vital signs and adverse reactions were checked at each blood sampling. Sumatriptan levels were determined by HPLC with electrochemical detection. Pharmacokinetic parameters were calculated using a computer programme (PK Solutions 2.0; Non-Compartmental Pharmacokinetics Data Analysis).

The following parameters were evaluated: elimination half-life ($t_{1/2}$), absorption half-life ($A_t$), peak plasma concentration ($C_{max}$), time to peak plasma concentration ($t_{max}$), area under the plasma concentration computed using observed data points only ($AUC_{O,obs}$), area under the plasma concentration computed using data points extrapolated to infinity ($AUC_{O,inf}$), mean residence time, time for 63.2% of administered dose to be eliminated (MRT), apparent volume of distribution (Vd) and systemic clearance (Cl). The relative values of AUC after oral sumatriptan administration and AUC after subcutaneous administration, referred to unit dose, provide the relative oral bioavailability of the drug.

## Results

The pharmacokinetic parameters obtained following subcutaneous administration of sumatriptan (6 mg) (Table 1) were found to be within the ranges reported in previous studies [6], and to confirm at the same time the minimal inter-individual variability of plasma concentrations of the drug in all three patient groups. The statistical analysis failed to show

### Methods

So far, we determined sumatriptan pharmacokinetics in the following migraine patients: group 1, 3 females (mean age±SD: 51.5±12.0 years), who obtained headache relief; group 2, 3

### Table 1 Pharmacokinetic parameters (mean±SD) of sumatriptan in migraine patients following 6 mg subcutaneous administration

| Group | $t_{1/2}$, h | $A_t$, h | $C_{max}$, ng/ml | $t_{max}$, min | $AUC_{O,obs}$, ng/min/ml | $AUC_{O,inf}$, ng/min/ml | MRT, min | Vd, ml/kg | Cl, ml/min/kg |
|-------|--------------|----------|-----------------|----------------|--------------------------|--------------------------|---------|------------|--------------|
| 1st   | 70.0±16.0    | 1.5±0.5  | 79.5±37.9       | 7.5±3.5        | 3106.8±1546.3            | 3575.5±1381.8            | 69.0±13.4 | 3045.5±466.8 | 31.5±11.8    |
| 2nd   | 73.1±8.6     | 2.7±1.5  | 50.5±17.6       | 15.0±7.1       | 4648.9±2911.2            | 5158.0±2628.9            | 105.0±9.8 | 1923.1±1200.5| 17.7±9.2     |
| 3rd   | 66.5±18.9    | 2.9±2.5  | 55.6±5.3        | 12.5±3.5       | 3924.2±544.3             | 4121.7±476.9             | 76.5±15.9 | 2339.8±346.3 | 24.9±3.5     |

### Table 2 Pharmacokinetic parameters (mean±SD) of sumatriptan in migraine patients following 100 mg oral administration

| Group | $t_{1/2}$, h | $A_t$, h | $C_{max}$, ng/ml | $t_{max}$, min | $AUC_{O,obs}$, ng/min/ml | $AUC_{O,inf}$, ng/min/ml | MRT, min | Vd, ml/kg | Cl, ml/min/kg |
|-------|--------------|----------|-----------------|----------------|--------------------------|--------------------------|---------|------------|--------------|
| 1st   | 90.9±39.5    | 39.9±5.5 | 44.7±4.4        | 110.0±17.3     | 9357.1±2393.9            | 11910.6±5208.6           | 219.3±39.9 | 14341.3±660.7| 132.9±108.4  |
| 2nd   | 84.4±11.8    | 41.1±9.1 | 48.4±1.6        | 165.0±106.1    | 11908.2±108.7            | 14672.6±1688.4           | 247.6±51.0 | 10914.9±470.1| 90.2±8.7     |
| 3rd   | 67.0±11.2    | 43.4±31.0| 58.9±6.1        | 180.0±127.3    | 9606.0±371.2             | 11301.2±1935.6           | 222.6±81.3 | 7261.4±208.4 | 76.3±14.9    |
any significant difference for all kinetic parameters following subcutaneous administration. Our results agree with those obtained in non-respondent subjects [7].

Also, the pharmacokinetic parameters obtained following oral administration of sumatriptan 100 mg (Table 2) conform to those reported in the literature [6]. No evidence of significant differences between patients was found. Comparison between relative oral bioavailability of sumatriptan for the three patient groups showed a tendential, but non-significant decrease in the amount of the available drug. The differences of average increase of arterial pressure values between respondent and non-respondent patients were not significant. Heart rate remained quite stable (practically unchanged) in all patients.

Conclusions

Our study shows that pharmacokinetic parameters and bioavailability of sumatriptan did not seem to be correlated either to the lack of efficacy or the appearance of side effects. These results could depend on the limited number of patients studied up to now.

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