BIBLID: ISSN 0253-9756 中国药理学报 *Acta Pharmacologica Sinica* 1992 Jul; 13 (4) : 298-301

Serum concentration fluctuation and bioavailability comparison between indomethacin sustained-release and conventional capsules during steady state

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ABSTRACT The comparison between indomethacin conventional capsule (CC) *po* 25 mg q 8 h or 25 mg tid and indomethacin sustained-release capsule (SRC) *po* 25 mg bid in human by crossover design showed that both maximal serum concentration (C_{max}) and fluctuation index (FI%) of SRC were significantly lower than those of CC during steady state ($P<0.01$). No practical differences were observed between the 2 preparations in the trough serum concentration (C_{min}) and area under serum concentration-time profiles ($AUC_{0-\tau}$) ($P>0.05$). The time period reaching maximal serum concentration (T_{max}) of SRC was much more delayed than that of CC ($P<0.01$). It suggested that SRC possesses a better controlled release property and could avoid a higher serum peak concentration of CC.

KEY WORDS indomethacin; biological availability; delayed-action preparations

Indomethacin, a nonsteroid anti-inflammatory agent, possesses a remarkable therapeutic effect for arthronosis deformans. When patients have been taking a conventional capsule (CC) 25-50 mg (tid) for a long time, about 10-20% of them have to discontinue the drug because of gastrointestinal or central nervous system adverse reactions[1-2]. The latter were associated with higher peak blood concentration of indomethacin[3]. The effective blood concentration range of indomethacin is 0.3-3.0 $\mu g \cdot ml^{-1}$ [4]. The sustained release indomethacin capsule (SRC, 50 mg), a multiple-unit controlled release formulation and a conventional slow release formulation, could avoid a higher serum peak concentration and showed significantly higher drug concentration in serum at 4-12 h following a single dose compared with CC 50 mg[5]. This study was to compare *po* SRC 25 mg q 12 h with CC 25 mg q 8 h or 25 mg tid in the serum concentration-time profile, serum concentration fluctuation index (FI%) and bioavailability during steady state.

Received 1991 Oct 24 Accepted 1992 May 6
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MATERIALS AND METHODS

Drug SRC and CC were supplied by Shanghai Yan-an Pharmaceutical Factory and Shanghai № 21 Pharmaceutical Factory, respectively. Each capsule contains 25 mg indomethacin.

Subjects Eight healthy young male volunteers (aged 23.0 ± *s* 0.2 a, weighing 60.7 ± 5.7 kg) took no other medicine 2 wk before and during the study. All volunteers were fasted 2 h before and after the administration and took the same diet during the study.

Study design The study was conducted in a randomized, two-way and crossover design. The volunteers took 25 mg SRC bid (07:00, 19:00) or 25 mg CC q 8 h (07:00, 15:00, 23:00), 2 preparations lasted for 7-8 d. At d 5-8, the blood samples were collected just before administration (0 h) and at the time of peak serum concentration (T_{max}). The T_{max} of SRC and CC were estimated at 4 and 2 h respectively depending on the results of single dosing[5]. After the last dosing, the blood samples were collected at 0, 2, 3, 4, 5, 6, 8, 12 and 0, 1, 2, 3, 4, 6, 8 h, respectively, and were centrifuged (2000 × *g* 15 min). The serum was stored at -20 ℃ until assayed. Indometacin serum concentration was measured by reverse HPLC[6].

After the first period ended, the volunteers rested for 1 wk and continued the trial 7–8 d depending on the crossover design.

Another 2 volunteers took 25 mg CC tid (08:00, 12:00, 16:00) 7 d continuously in order to compare tid with q 8 h in serum concentration–time profile and FI% of indomethacin during steaty state.

Calculation and statistic The serum concentration–time curves were described in each subject during the last 6 dosings by the following pharmacokinetic variables: C_{min} (serum trough concentration), C_{max} (maximal serum concentration), T_{max} (time of reaching maximal serum concentration after administration), $AUC_{0-\tau}$ (area under serum concentration–time curve of a dosing interval, where τ is the dosing interval). The data were calculated by an IBM computer in the parabolic and trapezoid method. And FI% (fluctuation index) was expressed as follows:

$$FI = (C_{max} - C_{min}) \cdot [1/2(C_{max} + C_{min})]^{-1} \times 100\%$$

For the pharmacokinetic parameters, the comparisons between SRC and CC were carried out by pairwise *t* test.

RESULTS

Mean serum concentration–time curves during steady state for both formulations were shown in Fig 1. The pharmacokinetic parameters derived from the individual concentration data were summarized in Tab 1. The results show that serum concentration–time profiles of SRC were smoother than those of CC, which was confirmed by the derived pharmacokinetic parameter and their statistical analysis.

Tab 1. Pharmacokinetic parameters of indomethacin at steady state between 5–8 d after *po* 25 mg indomethacin sustained–release capsule bid or conventional capsule q 8 h in 6 volunteers. $\bar{x} \pm s$, $^{*}P>0.05$, $^{***}P<0.01$.

		Sustained–release	Conventional
C_{min} / μg · ml^{-1}		0.36 ± 0.06	0.45 ± 0.18*
C_{max} / μg · ml^{-1}	a	0.70 ± 0.08	1.3 ± 0.3***
	b	0.80 ± 0.10	1.5 ± 0.3***
FI / %		65 ± 5	100 ± 15***
T_{max} / h		4.0 ± 0.4	2.11 ± 0.23***
$AUC_{0-\tau}$ / μg · h · ml^{-1}		5.4 ± 1.0	5.9 ± 1.9*

a) During the last 6 dosings.
b) At the last dosing.

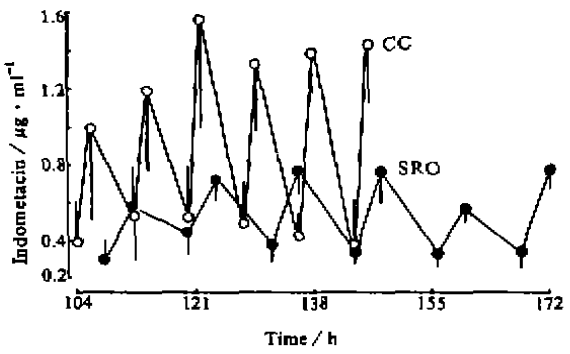

Fig 1. Indomethacin concentrations in serum between 5–8 d after *po* 25 mg indomethacin sustained–release capsule bid and conventional capsule q 8 h in 6 volunteers.

The C_{max} values of SRC were significantly lower than those of CC ($P<0.01$). However, no significant differences were observed between C_{min} values of the 2 formulations. As a result, the serum level FI% of SRC was very significantly smaller than that of CC ($P<0.01$). The T_{max} values of SRC were much longer than that of CC ($P<0.01$).

The relative bioavailability indicated by $AUC_{0-\tau}$ of the 2 formulations was approximately the same.

Shown in Fig 2 was the serum concentration–time curve during steady state representing another two volunteers' results. After morning dosing, C_{max} was 1.12 ± 0.10 μg · ml^{-1} and significantly higher than that at noon ($P<0.05$) and 4 pm ($P<0.01$), the FI% (144 ± 13%) was the largest in the study. Before morning dosing, C_{min} (0.18 ± 0.04 μg · ml^{-1}) was the lowest in the study and was below the effective therapeutic level.

DISCUSSION

The differences of C_{max}, C_{min}, and FI%

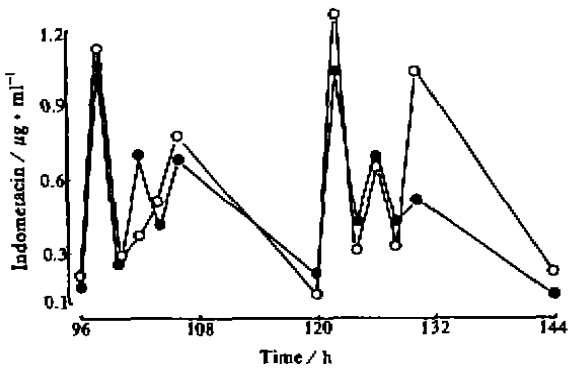

Fig 2. Indomethacin concentrations in serum between d 5–7 after 2 volunteers *po* 25 mg indomethacin conventional capsules tid.

between the 2 indomethacin formulations showed that SRC produced a smoother and more sustained serum concentration–time profile than that of CC during steady state, indicating that SRC possesses the properties of prolonged dissolution and absorption. The ranges of mean concentration (s) of SRC (25 mg, bid) and CC (25 mg, q 8 h) were: The former was 0.36 (0.06)–0.70 (0.08) $\mu g \cdot ml^{-1}$, the latter, 0.45 (0.18)–1.32 (0.30) $\mu g \cdot ml^{-1}$. Although all of them fall within the range of effective therapeutic blood concentration, SRC could reduce the higher peak blood concentration of CC and prolong the dosing interval.

Actually measured T_{max} of SRC and CC were 3.95 ± 0.35 h and 2.11 ± 0.23 h respectively after the last dosing, whereas their corresponding C_{max} were 0.80 ± 0.10 and 1.46 ± 0.32 $\mu g \cdot ml^{-1}$, respectively. The similar $AUC_{0-\tau}$ values and the differences in T_{max} and C_{max} illustrated that the 2 preparations share the same bioequivalency at steady state and SRC possesses a good controlled release property.

For the morning *po* CC 25 mg tid, it brought about the following drawbacks: the largest FI% and the lowest C_{min} which causes indomethacin serum concentration just below the effective therapeutic range. According to Francis *et al*[7], the morning dosing was responsable for a 32% incidence of undesirable effects, whereas the comparable rate was 7% for the evening dosing. Since tid is more widely used in clinical practice than q 8 h, and tid may produce the above mentioned drawbacks, we suggested that SRC (bid) could be recommended to replace CC (tid) in clinical practice because it will be much convenient for its clinical application besides its lower FI%, smoother concentration–time profile and equivalent bioavailability. In conclusion, SRC has a good controlled release property.

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吲哚美辛缓释胶囊与普通胶囊稳态血浓度波动指数及生物利用度比较

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提要 6名志愿者交叉服用吲哚美辛缓释胶囊(25 mg bid)与普通胶囊(25 mg q 8 h)稳态血药浓度的波动指数(FI%)和生物利用度比较。结果表明，两种制剂的血药谷浓度和吸收程度相近($P>0.05$)，但缓释胶囊的血药峰浓度和FI(%)均明显小于普通胶囊($P<0.01$)。达峰时间也明显较迟($P<0.01$)，提示缓释胶囊有较好的缓释特性。

关键词 吲哚美辛；生物利用度；迟效制剂

BIBLID: ISSN 0253-9756 中国药理学报 *Acta Pharmacologica Sinica* 1992 Jul; 13 (4) · 301-306

Effects of ohmefentanyl on CA1 field potentials in rat hippocampus slices

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ABSTRACT The effects of ohmefentanyl (OMF), a new opiate agonist with high affinity and high specificity for μ receptors, was examined on CA1 field potentials in the transverse hippocampal slices. OMF showed two effects upon the evoked population spikes (PS) recorded in stratum pyramidale: 1) a concentration-dependent increase in the amplitude of PS, which was largely reversed by naloxone, and 2) production of a naloxone-reversible additional PS at high stimulus intensities. No significant change was seen in field excitatory postsynaptic potential (EPSP) recorded simultaneously in stratum radiatum. The EC_{50} for OMF and morphine were 6.6 and 3700 nmol · L^{-1}, respectively. Thus OMF was 560 times more potent than morphine. The mechanism of augmentation by OMF of PS could be attributed to disinhibition as judged from the paired-pulse paradigm.

KEY WORDS ohmefentanyl; morphine; naloxone; hippocampus; evoked potentials

The rat hippocampus contained the major forms of endogenous opioid peptides as well as μ, δ, and κ opioid receptor types[1]. Opioid receptors were located in CA1, CA3, and the dentate gyrus[1,2]. Within each area, the density of receptors was found to be highest in and near the stratum pyramidale and granulosum, and all 3 major types of opioid receptors were increased in these layers. In the hippocampus, excitatory effects induced by opiates were found in CA1, CA3, and dentate gyrus. Opiate alkaloids or peptides applied to the hippocampus *in vivo* or *in vitro* increased the size of evoked field potentials[3-6]. It has been suggested that the δ receptor was the predominant receptor involved, inasmuch as [*D*-Ala^2, *D*-Leu^5]enkephalin (a relatively δ selective agonist) was more potent than morphine in producing the effect and morphine was considered to be the prototypic agonist for μ receptor[3].

OMF is a potent analgesic derived from fentanyl and was synthesized first in our laboratory[7]. The receptor binding assay and the assay carried out in isolated preparations indicated that OMF showed a high affinity and specificity for μ opioid receptor, and it was better than [*D*-Ala^2, MePhe^4, Gly-ol^5]enkephalin as a μ ligand[7-10]. Our aim was to characterize the pharmacological effects of OMF in the hippocampus slices and to assess the relationship between μ receptor and increased excitability of pyramidal cells using OMF, a novel and highly specific μ agonist.

Received 1991 Dec 4 Accepted 1992 Mar 26