Relative Bioavailability and Pharmacokinetics: A Combination of Pentazocine and Acetaminophen

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Abstract □ The relative bioavailability and pharmacokinetics of a combination product containing pentazocine and acetaminophen were studied in 20 healthy human males. Each subject, in a single-dose three-way crossover design, received two different preparations containing 50 mg of pentazocine (as base) and 1300 mg of acetaminophen either as capsule-shaped tablets or as a solution. Plasma concentrations of pentazocine and acetaminophen were determined from 0.25 to 12 h following oral administration. The plasma data for both compounds in the tablet formulation were described by an open one-compartment body model with first-order absorption. The average ($\pm SD$) bioavailability of the tablet relative to that of the solution was 85.0 ± 31.1 and 88.6 ± 13.1% for pentazocine and acetaminophen, respectively. The apparent first-order regression-dependent elimination rate constants for pentazocine from the tablet and solution preparations were 0.19 ± 0.08 and 0.20 ± 0.06 h^{-1}, respectively, while the rate constants for acetaminophen were 0.26 ± 0.03 and 0.25 ± 0.03 h^{-1} for the tablet and solution preparations, respectively. These rate constants correspond to terminal elimination half-lives of ~3.6 h for pentazocine and ~2.7 h for acetaminophen.

Keyphrases □ Pentazocine—relative bioavailability, pharmacokinetics, coadministration with acetaminophen □ Acetaminophen—relative bioavailability, pharmacokinetics, coadministration with pentazocine □ Bioavailability—relative, coadministered pentazocine and acetaminophen, pharmacokinetics □ Pharmacokinetics—coadministered pentazocine and acetaminophen, relative bioavailability

Pentazocine, a weak narcotic antagonist, is a potent analgesic in humans. The analgesic efficacy of both oral (1, 2) and parenteral (3–8) formulations of pentazocine is well documented. Acetaminophen is commonly used as a mild analgesic and antipyretic (9, 10). Both pentazocine and acetaminophen have low incidences of adverse side effects at therapeutic dosages (3, 9, 10).

Since pentazocine is thought to act centrally and acetaminophen acts primarily peripherally, the simple additive effect of a narcotic antagonist and an antipyretic–analgesic given together may be substantially greater than the analgesia obtained from each component separately (11, 12). In our investigation, the bioavailability and pharmacokinetic parameters of pentazocine and acetaminophen were determined in human subjects following administration of two different preparations of pentazocine combined with acetaminophen.

EXPERIMENTAL

Subjects—The subjects were 20 healthy male volunteers, ranging in age from 19 to 33 years and in weight from 53 to 104 kg. No subject had a clinical history or laboratory findings that were suggestive of renal, hepatic, or cardiac dysfunction. Appropriate institutional review and approval were obtained.

Drug Administration and Sampling—Each subject received two different preparations of pentazocine and acetaminophen in a single dose according to a randomized three-way crossover design. One dose was two capsule-shaped tablets[1], each containing 25 mg of pentazocine base and 650 mg of acetaminophen, and the other dose was a solution containing 50 mg of pentazocine base and 1300 mg of acetaminophen (prepared in-house). For the third dose, one-half of the subjects received a repeat dose of the solution and the other half of the subjects received a repeat dose of the tablets. There was a 1-week washout interval between medications. Blood samples were collected by venipuncture prior to drug administration and at 0.25, 0.50, 0.75, 1, 2, 4, 6, 7 and 12 h after treatment; potassium oxalate was used as the anticoagulant. All subjects were fasted for at least 8 h before treatment and 3 h afterwards. Blood samples were centrifuged, and the plasma was separated and frozen until it was assayed.

Analytical Methods—Pentazocine plasma concentrations were determined using a minor modification of the RIA procedure (13) developed in these laboratories; toluene was used for the extraction in place of benzene. The minimum quantifiable level of the assay was estimated as the concentration whose lower 95% confidence limit just encompassed zero and was ~0.4 ng/mL. Blind analyses of plasma samples spiked with pentazocine over the range of 0 and 0.4 to 100 ng/mL revealed a mean intraassay variation coefficient of 8.2% (n = 18) and a mean interassay coefficient of variation of 11.6% (n = 3).

Plasma concentrations of acetaminophen were determined by the HPLC method reported by Horwitz and Jatlow (14), with the following modifications. Plasma was extracted with 7 mL of diethyl ether instead of 5 mL. The residue remaining after evaporation of the solvent was dissolved in 200 μL of the mobile phase, and 50 μL were injected onto a 3.9-mm i.d. × 30-cm phenyl column[2] using a solvent system of 7% acetonitrile in 0.1 M KH_2PO_4 (v/v) adjusted to pH 2.4 with phosphoric acid. The flow rate was increased to 2.0 mL/min. The mean quantifiable level for acetaminophen was estimated by linear regression of the peak-height ratios as the concentration whose lower 80% confidence limit just encompassed zero (15) and was between 0.02 and 0.06 μg/0.5 mL. Blind analyses of acetaminophen standards prepared with human control plasma over the range of 0 and 0.1 to 15 μg/0.5 mL yielded an intraassay coefficient of variation (precision) of ±4.9% (n = 2). The accuracy of the assay, defined as the mean percent difference from a nominal value, ranged from −7.5 to 3.0% (n = 18).

Pharmacokinetic Calculations—Pharmacokinetic parameters for pentazocine and acetaminophen were derived by analysis of the plasma concentration data by means of a weighted nonlinear regression procedure (NLIN) using the Marquardt algorithm (16). The plasma concentrations were weighted as the squares of their reciprocals (17, 18). Where appropriate, results are expressed as the mean $\pm SD$.

The plasma data obtained for pentazocine (tablet and solution) and acetaminophen (tablet) was fitted to an open one-compartment body model with first-order absorption and was described by the following:

$$C = A[e^{-k_e(t-t_0)} - e^{-k_a(t-t_0)}] \qquad \text{(Eq. 1)}$$

where C is the plasma concentration at time, t, t_0 is the lag time (before absorption begins), A is a constant, and k_a and k_e are apparent first-order rate constants for absorption and elimination, respectively. Since the absorption of acetaminophen in solution is very rapid, the data from the analysis of the acetaminophen solution dose was fit to a one-compartment open model assuming instantaneous absorption (intravenous model) by means of a weighted regression analysis as above, and was described by the following:

$$C = B(e^{-k_e t}) \qquad \text{(Eq. 2)}$$

where B is a constant and the other terms are defined above.

The apparent volume of distribution (uncorrected for bioavailability), Vd/F, which relates the plasma concentration to the total amount of drug in the body, was calculated by the use of the following:

$$Vd/F = \frac{\text{Dose} \cdot k_a}{A(k_a - k_e)} \qquad \text{(Eq. 3)}$$

[1] Talacen; Winthrop Laboratories, New York, N.Y.

[2] μ-Bondapak CN; Waters Associates, Milford, Mass.

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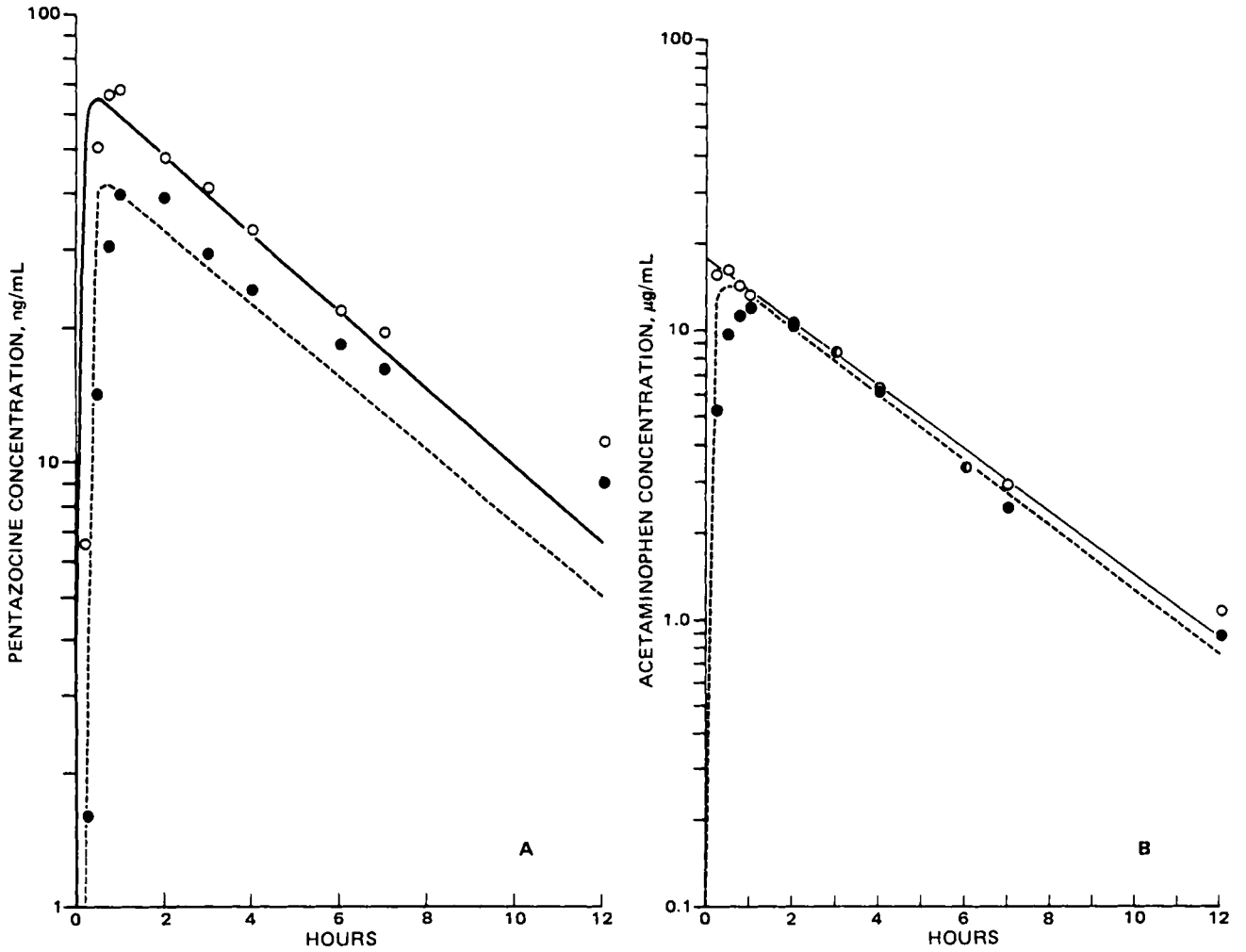

Figure 1—*Mean plasma concentrations of pentazocine (A) and acetaminophen (B) in 20 human volunteers after oral administration of either two tablets (●) or a solution (○) containing 50 mg of pentazocine and 1300 mg of acetaminophen. The lines represent the respective model-dependent curves derived from the mean pharmacokinetic parameters.*

$$Vd/F = \frac{\text{Dose}}{C_0} \qquad \text{(Eq. 4)}$$

where F is the fraction of the administered dose which is available to the systemic circulation; the other terms are defined above. The apparent total plasma clearance (CL_p) relates to drug availability (F) and was calculated from:

$$\frac{CL_p}{F} = \frac{\text{Dose}}{\text{AUC}_0^\infty} \qquad \text{(Eq. 5)}$$

The total area under the plasma concentration *versus* time curve (AUC_0^∞) for each subject was determined from the following:

$$\text{AUC}_0^\infty = \frac{A(k_a - k_e)}{k_a k_e} \qquad \text{(Eq. 6)}$$

$$\text{AUC}_0^\infty = \frac{F \cdot \text{Dose}}{Vd \cdot k_e} \qquad \text{(Eq. 7)}$$

In addition to the regression-dependent parameters (defined above), the plasma concentration data were analyzed with respect to the following regression-independent parameters: the maximum observed plasma concentration (C_{max}^{obs}), the time at which the maximum plasma concentration was observed (t_{max}^{obs}), and AUC_0^{12}. The latter was calculated by the trapezoidal rule, including all of the data for the study period. For those subjects who had detectable concentrations of pentazocine or acetaminophen in the last sample examined, the AUC was extrapolated to infinite time by use of the following:

$$\text{AUC}_0^\infty = \text{AUC}_0^{12} + \frac{C_p}{k_t} \qquad \text{(Eq. 8)}$$

where C_p was the pentazocine or acetaminophen concentration observed in the last measurable sample taken and k_t is the estimated apparent first-order terminal elimination rate constant; k_t was estimated by linear regression on the natural logarithms of the observed plasma concentration from t_{max} to the last data point.

The regression-independent volume of distribution (uncorrected for bioavailability), Vd/F, was determined by the following equation:

$$Vd/F = \frac{\text{Dose}}{k_t \cdot \text{AUC}_0^\infty} \qquad \text{(Eq. 9)}$$

The bioavailability of the tablet doses relative to that of the solution doses was determined from the ratio of their respective extrapolated AUC values:

$$\text{Relative bioavailability} = \frac{\text{AUC}_0^\infty \text{ (tablet)}}{\text{AUC}_0^\infty \text{ (solution)}} \times 100 \qquad \text{(Eq. 10)}$$

RESULTS

Pentazocine—The plasma levels of pentazocine for each subject declined exponentially with time and were best fit with an open one-compartment body model with first-order absorption. The mean plasma concentrations are shown in Fig. 1A. The mean apparent first-order elimination rates for the tablet and solution were 0.19 ± 0.08 and 0.20 ± 0.06 h^{-1}, respectively, which corresponds to a half-life of ~3.6 h for both the tablet and solution preparations. Results are shown in Tables I and II, respectively.

The apparent volume of distribution showed considerable variation between individuals for both preparations. The mean apparent Vd/F for the tablet was 1614 L, with a range of 495–4906 L, and the solution had a mean apparent Vd/F of 1177 L, with a range of 243–2865 L. Plasma clearance (CL_p) and the first-order absorption rate (k_a) demonstrated considerable intersubject variation. The mean AUC_0^∞ values for the tablet

Table I—Pharmacokinetic Parameters Derived from Pentazocine Plasma Data from Subjects Receiving Tablets Containing Pentazocine and Acetaminophen

	Model Independent						Regression Dependent						
Subject	t_{max}^{obs}, h	C_{max}^{obs}, ng/mL	Vd/F, L	CL_p/F, L·h^{-1}	AUC_0^{12}, ng·h/mL	k_t, h^{-1}	A, ng/mL	k_a, h^{-1}	k_e, h^{-1}	t_0, h	Vd/F, L	CL_p/F, L·h^{-1}	AUC_0^{∞}, ng·h/mL
101	2.0	86	645	148	306	0.23	68.3	1.24	0.21	0.24	879	183	273
101	1.0	35	1302	235	184	0.18	39.8	4.51	0.19	0.46	1311	244	205
102	2.0	94	549	27.5	821	0.05	79.1	52.7	0.03	0.25	633	19.8	2528
102	2.0	162	426	34.1	866	0.08	63.7	2.77	0.07	0.48	495	34.9	1432
103	2.0	21	2140	342	121	0.16	27.2	1.10	0.17	0.39	2165	360	139
103	0.75	41	1502	301	150	0.20	32.9	63.8	0.20	0.50	1525	301	166
104	1.5	24	1754	420	110	0.24	29.4	2.45	0.24	0.19	1887	459	109
104	1.0	62	926	222	208	0.24	55.3	1.25	0.24	0.24	1114	263	190
105	0.75	20	2591	521	86	0.20	20.8	2.51	0.21	0.24	2615	544	91.9
105	1.0	32	2088	481	95	0.23	21.3	52.9	0.23	0.47	2359	542	92.3
201	1.0	61	1129	237	188	0.21	39.3	2.32	0.19	0.48	1385	266	188
201	1.0	91	829	208	226	0.25	47.9	2.36	0.22	0.23	1152	256	195
202	0.5	52	1038	467	107	0.45	50.6	53.6	0.48	0.25	996	476	105
202	0.75	55	924	278	173	0.30	49.8	2.44	0.30	0.06	1144	342	146
203	7.0	38	740	118	316	0.16	25.1	52.8	0.02	0.49	1992	38.5	1300
203	1.0	62	963	202	218	0.21	45.4	6.43	0.21	0.49	1138	235	213
204	3.0	9.0	4386	526	70	0.12	12.2	1.25	0.11	—[a]	4498	510	98.1
204	0.75	8.0	5275	735	57	0.14	10.7	3.39	0.16	0.34	4906	780	64.1
205	3.0	63	764	99.4	357	0.13	61.4	1.27	0.14	0.48	918	133	376
205	3.0	45	824	140	304	0.17	63.5	1.51	0.17	0.47	889	153	327
301	1.0	25	1812	382	119	0.21	30.4	1.64	0.21	0.16	1894	406	123
302	1.0	38	1321	238	182	0.18	41.4	4.36	0.19	0.43	1263	244	205
303	1.0	121	448	49.3	688	0.11	107	1.53	0.11	0.24	503	55.9	895
304	2.0	28	1544	340	134	0.22	33.2	1.85	0.22	0.24	1711	382	131
305	1.0	61	1019	214	208	0.21	50.8	60.5	0.24	0.25	989	234	214
402	2.0	27	1600	305	144	0.19	33.9	1.42	0.19	0.42	1698	314	159
403	2.5	18	2154	345	122	0.16	28.1	1.31	0.18	0.46	2059	362	138
404	0.75	19	2796	336	114	0.12	17.9	59.5	0.12	0.48	2800	340	147
405	2.0	68	617	148	315	0.24	93.5	1.56	0.24	0.21	633	154	324
406	4.0	35	952	162	252	0.17	88.8	0.55	0.20	0.44	877	171	292
Mean	1.74	50.0	1502	275	238	0.19	45.6	14.9	0.19	0.35	1614	293	362
±*SD*	1.32	34.3	1105	164	211	0.07	24.2	23.5	0.08	0.13	1040	174	526

[a] No meaningful value; not included in the mean.

and solution preparations were 362 ± 526 and 404 ± 474 ng·h/mL, respectively. The calculated bioavailability of pentazocine in the tablet relative to the solution demonstrated considerable intrasubject variation, as well as significant interindividual variability, and ranged from 37.0 to 216% with a mean value of 85.0 ± 31.1%. Individual AUC_0^{∞} values and relative bioavailability data are presented in Table III.

The observed regression-independent parameters are in reasonable agreement with those estimated from the open one-compartment body

Table II—Pharmacokinetic Parameters Derived from Pentazocine Plasma Data from Subjects Receiving a Solution Containing Pentazocine and Acetaminophen

	Model Independent						Regression Dependent						
Subject	t_{max}^{obs}, h	C_{max}^{obs}, ng/mL	Vd/F, L	CL_p/F, L·h^{-1}	AUC_0^{12}, ng·h/mL	k_t, h^{-1}	A, ng/mL	k_a, h^{-1}	k_e, h^{-1}	t_0, h	Vd/F, L	CL_p/F, L·h^{-1}	AUC_0^{∞}, ng·h/mL
101	0.62	89	658	112	382	0.17	74.7	54.1	0.17	0.25	672	115	434
102	1.0	166	229	27	1055	0.12	99.8	5.39	0.04	0.24	505	21	2431
103	2.5	20	1921	327	129	0.17	31.5	1.29	0.19	0.45	1854	345	145
104	1.0	28	1749	333	131	0.19	28.7	2.31	0.19	0.23	1895	352	142
105	0.50	37	1869	485	96	0.26	24.6	56.0	0.26	0.25	2041	523	95.6
201	3.0	32	1082	216	202	0.20	48.8	1.27	0.19	0.23	1207	232	216
202	0.75	85	820	221	214	0.27	52.7	9.16	0.26	0.21	976	250	200
203	0.75	36	1279	255	174	0.20	44.0	3.98	0.28	0.20	1224	247	144
204	0.75	16	3173	413	95	0.13	18.3	2.03	0.15	0.20	2941	435	115
205	0.75	127	665	80	443	0.12	72.9	6.67	0.11	0.21	889	76	654
301	0.75	38	1279	320	148	0.25	38.0	56.9	0.25	0.25	1320	329	152
301	0.75	56	1348	300	155	0.22	34.0	56.6	0.21	0.48	1475	311	161
302	0.75	46	914	182	248	0.20	65.1	1.96	0.22	0.16	864	189	265
302	0.75	99	638	153	301	0.24	72.4	8.95	0.23	0.24	709	162	309
303	2.0	120	374	49	790	0.13	145	1.50	0.13	0.25	379	50	1000
303	0.75	203	254	38	1033	0.15	186	2.74	0.15	0.24	285	44	1136
304	0.50	83	1243	300	153	0.24	32.9	72.1	0.22	0.24	1524	340	147
304	0.87	53	1073	258	180	0.24	42.1	51.7	0.23	0.24	1192	273	183
305	1.0	58	855	171	262	0.20	55.2	17.5	0.19	0.23	917	177	283
305	1.0	131	549	143	327	0.26	94.3	52.4	0.31	0.25	533	166	301
402	2.5	34	1142	251	179	0.22	47.2	1.33	0.21	0.16	1260	267	187
402	1.0	54	1066	224	200	0.21	45.3	4.09	0.21	0.23	1163	238	210
403	0.75	35	1567	312	142	0.20	32.7	49.5	0.21	0.25	1535	318	157
403	0.50	42	1582	316	140	0.20	30.2	63.2	0.19	0.25	1661	320	156
404	2.0	26	1691	287	148	0.17	31.2	1.64	0.17	0.24	1787	303	165
404	0.75	21	2797	391	102	0.14	18.2	3.29	0.14	0.24	2865	397	126
405	0.75	162	275	66	707	0.24	187	5.36	0.25	0.21	280	69	727
405	1.0	219	236	61	768	0.26	222	3.78	0.27	0.23	243	65	772
406	1.0	49	792	127	335	0.16	79.7	1.07	0.19	0.20	761	142	351
406	0.75	214	285	60	744	0.21	147	61.5	0.20	0.25	342	67	746
Mean	1.06	79.3	1140	216	333	0.20	70.0	22.0	0.20	0.20	1177	227	404
±*SD*	0.65	61.1	721	123	283	0.04	54.4	25.9	0.06	0.06	128	129	464

Table III—Relative Bioavailability of Tablet Compared to Solution Based on Regression-Independent AUC_0^∞ Data

Subject	Pentazocine			Acetaminophen		
	AUC_0^∞, ng·h/mL		Relative	AUC_0^∞, μg·h/mL		Relative
	Tablet	Solution	Bioavailability	Tablet	Solution	Bioavailability
101	337	447	75.4	51.2	67.5	75.8
101	213	—	47.8	56.4	—	83.6
102	1821	1822	100	49.2	53.4	92.1
102	1466	—	80.5	56.9	—	107
103	146	153	95.4	88.5	89.9	98.5
103	166	—	109	93.4	—	104
104	118	150	78.9	53.6	55.3	96.9
104	225	—	120	60.9	—	110
105	96	103	93.8	45.7	54.1	84.4
105	104	—	101	51.2	—	94.7
201	211	231	91.3	71.6	75.8	94.6
201	241	—	104	93.0	—	123
202	107	226	47.4	65.8	74.4	88.4
202	180	—	79.8	59.5	—	80.0
203	422	196	216	61.4	66.7	92.1
203	248	—	127	66.7	—	100
204	95	122	78.2	56.7	59.5	95.3
204	68	—	55.7	60.8	—	102
205	503	626	80.3	40.6	66.2	61.0
205	357	—	57.0	41.2	—	62.2
301	131	156	84.0	63.2	67.4	93.6
301	—	169	77.9	—	73.9	85.4
302	210	274	76.9	57.2	68.9	83.1
302	—	327	64.4	—	83.6	68.5
303	1015	1028	98.7	54.1	60.3	89.7
303	—	1313	77.3	—	64.0	84.5
304	147	168	87.8	53.3	64.0	83.2
304	—	194	75.8	—	65.8	81.0
305	234	292	79.9	61.6	62.8	98.1
305	—	350	66.8	—	68.6	89.8
402	164	199	82.7	54.9	60.5	90.8
402	—	223	73.7	—	63.7	86.2
403	145	160	90.8	61.8	60.0	103
403	—	158	91.8	—	64.7	95.6
404	149	174	85.7	73.8	85.8	86.0
404	—	128	117	—	86.4	85.4
405	338	757	44.6	78.7	102	77.0
405	—	814	41.4	—	103	76.2
406	309	394	78.4	57.1	68.8	83.0
406	—	834	37.0	—	97.3	58.7
Mean	332	406	85.0	61.3	77.1	88.6
±*SD*	401	404	31.1	13.3	13.6	13.1

model with first-order absorption. The C_{max} values for the tablet and solution preparations were 50 ± 34.3 and 79.3 ± 61.1 ng/mL, respectively, and their respective t_{max} values occurred at 1.74 ± 1.32 and 1.06 ± 0.65 h. The regression-independent $t_{1/2}$ values for the tablet and solution preparation were identical to the regression-dependent $t_{1/2}$ values.

Acetaminophen—As seen in Fig. 1B, the plasma levels of acetaminophen in volunteers receiving the tablet declined exponentially with time, suggesting that an open one-compartment body model with first-order absorption would be appropriate. The plasma levels of acetaminophen in volunteers receiving the solution declined exponentially and were best described by a one-compartment body model assuming instantaneous absorption (intravenous model). The mean apparent first-order elimination rates for the tablet and solution were 0.26 ± 0.03 and 0.25 ± 0.03 h^{-1}, respectively, which corresponds to a $t_{1/2}$ of 2.7 h. The pharmacokinetic parameters are shown in Tables IV and V.

The mean apparent volume of distribution (Vd/F) for the tablet and solution were 90.3 ± 17.2 and 76.5 ± 14.7 L, respectively. Clearance of the tablet varied from 14.6 to 37.9 L·h^{-1}, while the plasma clearance of the solution ranged from 12.4 to 24.6 L·h^{-1}. The mean AUC_0^∞ values for the tablet and solution formulation were 57.5 ± 13.0 and 72.0 ± 14.4 μg·h/mL, respectively.

The observed, regression-independent parameters are in reasonable agreement with those calculated from the regression-dependent parameters. The mean apparent first-order terminal elimination rate constants were 0.25 ± 0.04 and 0.24 ± 0.03 h^{-1}, respectively, for the tablet and solution preparations. The C_{max}^{obs} for the tablet data was 13.6 ± 3.7 μg/mL, and the respective t_{max}^{obs} occurred at 0.95 ± 0.64 h.

The calculated bioavailability of the tablet relative to the solution ranged from 58.7 to 123%, with a mean value of 88.6 ± 13.1%. Individual AUC_0^∞ values and relative bioavailability are presented in Table III. The regression-independent AUC_0^∞ for the solution data was in close agreement to that of the AUC_0^∞ calculated from the regression-dependent parameters. This suggests that the model which assumed instantaneous absorption was appropriate for the available data.

DISCUSSION

Pentazocine—Pharmacokinetic parameters for each subject were estimated after computer-fitting of the data by a weighted iterative nonlinear least-squares regression technique. The plasma data from each subject was best fit by an open one-compartment body model with first-order absorption. Attempts to fit the data from each subject to an open two-compartment body model with first-order absorption yielded residual sum-of-squares values significantly greater than the comparable values for an open one-compartment body model. The half-lives for the capsule-shaped tablet and solution data, 3.65 and 3.46 h, respectively, are similar to those reported by Ehrnebo *et al.* (19): 3.38 ± 1.18 and 2.95 ± 0.57 h, following intravenous and oral administration, respectively. The present values are in very close agreement with the mean half-life of 3.83 ± 0.47 h reported by Neal *et al.* (20) for four normal subjects. The elimination half-lives for the urinary excretion rate of intact pentazocine for a period of 24 h ranged from 2.0 to 5.5 h (21, 22), which are in accordance with our plasma values. The mean apparent Vd/F for the tablet and solution preparations were 1610 and 1110 L, respectively, or, dividing by the mean body weight, 21.4 and 14.7 L/kg. These values suggest that pentazocine may be bound or partition favorably into tissues. Ehrnebo *et al.* (19) and studies conducted in our laboratories[3] have demonstrated that first-pass metabolism of pentazocine after oral administration was ~80%. Taking this into account, one obtains mean estimates of 222 and 322 L for the tablet and solution treatments, which are in reasonable agreement with the range of 251–548 L reported by Ehrnebo *et al.* (19)

[3] Unpublished data.

Table IV—Pharmacokinetic Parameters Derived from Acetaminophen Plasma Data from Subjects Receiving Tablet Containing Pentazocine and Acetaminophen

	Model Independent						Regression Dependent						
Subject	t_{max}^{obs}, h	C_{max}^{obs}, μg/mL	Vd/F, L	CL_p/F, L·h^{-1}	AUC_0^{12}, ng·h/mL	k_t, h^{-1}	A, μg/mL	k_a, h^{-1}	k_e, h^{-1}	t_0, h	Vd/F, L	CL_p/F, L·h^{-1}	AUC_0^{∞}, ng·h/mL
101	1.0	12	90.8	25.4	48.8	0.28	16.2	2.09	0.30	0.18	93.6	27.8	46.7
101	0.50	14	82.3	23.0	54.1	0.28	15.3	49.0	0.29	0.25	85.4	25.0	52.0
102	0.25	15	94.4	26.4	47.2	0.28	12.2	a	0.27	0.18	106	29.0	44.9
102	1.0	12	104	22.8	52.5	0.22	12.8	2.66	0.22	0.15	111	23.9	54.3
103	2.0	12	77.3	14.7	78.0	0.19	18.6	1.73	0.19	0.17	78.5	14.9	87.5
103	0.75	15	81.9	13.9	80.5	0.17	23.3	1.46	0.24	0.11	67.0	16.3	79.9
104	0.75	15	80.9	24.2	51.7	0.30	16.6	6.70	0.31	0.02	82.3	25.2	51.5
104	0.75	17	76.3	21.4	58.2	0.28	18.0	3.33	0.28	0.22	78.8	22.2	58.7
105	0.25	11	105	28.4	43.5	0.27	11.8	43.9	0.28	0.18	111	30.7	42.3
105	0.50	14	94.0	25.4	48.6	0.27	13.5	52.6	0.27	0.22	96.8	26.3	49.5
201	1.0	13	82.5	18.2	65.7	0.22	18.9	1.67	0.24	0.22	80.2	19.0	68.3
201	0.75	24	51.7	14.0	88.6	0.27	26.0	5.37	0.28	0.18	52.6	14.7	88.7
202	0.25	16	75.9	19.8	63.2	0.26	17.4	15.3	0.27	—[a]	75.9	20.2	64.4
202	1.0	15	72.8	21.8	57.4	0.30	18.6	2.98	0.29	0.21	77.2	22.1	58.9
203	0.75	17	75.6	21.2	58.4	0.28	14.0	8.45	0.28	0.23	95.7	26.4	49.2
203	1.0	17	74.9	19.5	62.9	0.26	17.7	3.64	0.26	0.19	79.0	20.7	62.9
204	0.50	12	95.5	22.9	52.6	0.24	14.3	7.81	0.28	0.21	94.6	26.8	48.6
204	0.50	12	93.0	21.4	56.6	0.23	13.7	8.74	0.23	0.22	97.2	22.3	58.2
205	2.0	10	110	32.0	38.6	0.29	13.1	1.29	0.30	0.23	128	37.9	34.3
205	3.0	7.6	105	31.6	39.4	0.30	13.6	1.54	0.28	0.22	117	33.2	39.2
301	1.0	11	103	20.6	56.2	0.20	13.1	3.36	0.21	0.23	106	22.4	58.1
302	2.0	12	75.7	22.7	55.1	0.30	20.4	1.58	0.30	0.14	78.7	23.8	54.5
303	0.75	10	109	24.0	50.2	0.22	11.9	5.10	0.22	—[a]	114	24.9	52.2
304	0.50	11	97.6	24.4	50.6	0.25	14.0	5.22	0.26	0.12	97.5	25.2	51.6
305	0.25	24	70.3	21.1	59.4	0.30	17.6	—[a]	0.31	0.25	73.9	22.6	57.6
402	1.0	10	103	23.7	50.9	0.23	13.7	3.04	0.24	0.21	103	24.5	53.1
403	1.0	11	95.5	21.0	56.4	0.22	17.8	0.96	0.24	0.15	97.8	23.7	54.9
404	1.0	13	76.5	17.6	69.1	0.23	18.7	2.84	0.24	0.22	75.9	18.0	72.3
405	0.50	15	66.1	16.5	75.1	0.25	20.9	4.11	0.26	—[a]	66.3	17.1	76.1
406	2.0	9.6	99.0	22.8	52.8	0.23	21.7	0.80	0.26	0.16	89.2	14.6	89.2
Mean	0.95	13.6	87.4	22.1	57.4	0.25	16.5	8.83	0.26	0.19	90.3	23.4	57.5
±*SD*	0.64	3.7	14.6	4.4	11.6	0.04	3.6	14.4	0.03	0.05	17.2	5.4	13.0

[a] No meaningful value; not included in the mean.

and similar to those of Neal *et al.* (20), 342 ± 188 L, following intravenous administration of 0.8 mg/kg.

The regression-independent bioavailability of the tablet relative to that of the solution was 85.0 ± 31.1%. The AUC_0^{∞} values varied considerably among these volunteers by a factor of 28 and 15 for the tablet and solution, respectively. The data obtained from the solution did not show the same degree of intrasubject variation as that of the tablet. Others have observed the same interindividual variation (19, 21). In general, it has

Table V—Pharmacokinetic Parameters Derived from Acetominophen Plasma Data from Subjects Receiving a Solution Containing Pentazocine and Acetaminophen

	Model Independent						Regression Dependent				
Subject	t_{max}^{obs}, h	C_{max}^{obs}, μg/mL	Vd/F, L	CL_p/F, L·h^{-1}	AUC_0^{12} μg·h/mL	k_t, h^{-1}	C_0, μg/mL	k_e, h^{-1}	Vd/F, L	CL_p/F, L·h^{-1}	AUC_0^{∞}, μg·h/mL
101	0.50	19	71.4	19.3	64.4	0.27	18.6	0.28	69.9	19.4	67.1
102	0.50	16	87.0	24.3	51.2	0.28	15.0	0.28	86.4	24.0	54.2
103	0.75	15	65.7	14.5	84.4	0.22	20.0	0.22	64.9	14.4	90.6
104	0.50	13	87.1	23.5	52.6	0.27	15.3	0.28	85.1	23.5	55.4
105	0.25	22	89.0	24.0	51.1	0.27	14.7	0.28	88.3	24.6	52.8
201	1.0	15	71.5	17.2	70.8	0.24	19.6	0.25	66.3	16.4	79.5
202	0.25	20	62.4	17.5	71.5	0.28	21.1	0.28	61.6	17.1	75.9
203	0.50	19	72.2	19.5	63.5	0.27	18.8	0.28	69.0	19.3	67.3
204	0.75	11	99.4	21.8	55.0	0.22	13.2	0.22	98.7	21.4	60.7
205	0.25	28	89.3	19.6	58.4	0.22	17.3	0.26	75.2	19.3	67.5
301	0.25	16	83.8	19.3	62.7	0.23	16.1	0.24	80.9	19.3	67.5
301	0.50	22	79.9	17.6	66.6	0.22	17.6	0.23	74.0	17.2	75.8
302	0.25	18	72.5	18.9	65.5	0.26	17.2	0.26	75.6	19.5	66.6
302	0.25	24	55.6	15.6	80.2	0.28	23.9	0.28	54.4	15.2	85.4
303	0.50	15	86.2	21.6	56.7	0.25	15.5	0.25	83.3	21.0	61.8
303	0.25	18	84.6	20.3	59.8	0.24	15.9	0.24	82.0	20.0	65.0
304	0.25	20	81.2	20.3	60.1	0.25	16.0	0.25	81.3	20.2	64.2
304	0.25	28	76.0	19.8	62.1	0.26	16.1	0.25	81.0	20.1	64.8
305	0.25	22	69.0	20.7	60.8	0.30	19.3	0.30	67.3	20.2	64.5
305	0.25	32	65.4	20.0	65.6	0.29	19.7	0.29	66.1	19.2	67.7
402	0.25	11	97.7	21.5	55.9	0.22	12.0	0.21	108	22.5	57.8
402	0.25	17	81.7	20.4	59.7	0.25	16.5	0.26	78.8	20.1	64.6
403	0.50	10	108	21.7	54.5	0.20	11.9	0.20	110	22.0	59.2
403	0.50	15	95.7	20.1	59.5	0.21	14.0	0.21	92.9	19.8	65.8
404	0.75	16	68.8	15.2	79.5	0.22	19.6	0.22	66.5	14.7	88.7
404	2.0	16	60.2	15.0	81.6	0.25	21.4	0.23	60.6	14.2	91.6
405	0.25	22	53.0	12.8	96.3	0.24	24.3	0.24	53.5	12.6	103
405	0.50	26	50.4	12.6	98.0	0.25	26.3	0.25	49.4	12.4	105
406	1.0	11	89.9	18.9	63.1	0.21	15.2	0.21	85.6	18.1	71.7
406	0.50	22	78.6	13.4	82.0	0.17	16.3	0.16	79.6	13.1	99.1
Mean	0.49	18.6	76.5	18.8	66.4	0.24	17.6	0.25	76.5	18.6	72.0
±*SD*	0.36	5.5	13.2	3.2	12.5	0.03	3.5	0.03	14.7	3.3	14.4

been observed that the AUC values vary substantially for drugs with pronounced hepatic clearance, such as nortriptyline (23) and imipramine (24); the data suggest this is also true for pentazocine. In addition, the oral bioavailability of pentazocine was significantly enhanced in patients with cirrhosis of the liver, due to reduction in hepatic clearance (20, 25).

Acetaminophen—The plasma data obtained from the solution was fit to a one-compartment body model assuming instantaneous absorption because the first blood sample obtained, in the majority of the subjects, contained the highest level of acetaminophen, while the data obtained from the tablet treatment was fit to a one-compartment body model with first-order absorption. The half-lives for the tablet and solution, 2.67 and 2.77 h, respectively, are in close agreement with those reported by Lee *et al.* (26): 2.6 h in both obese and nonobese subjects. Divoll *et al.* (27) and Rawlins *et al.* (28) found that the mean half-life was 2.7 and 2.8 h after intravenous administration of 650 mg and 500 mg of acetaminophen, respectively. Others have reported half-lives ranging from 2.24 to 3.0 h (17, 29–34). Sotiropoulus *et al.* (35), based on urinary elimination of acetaminophen, reported half-lives of 2.77, 3.14, and 4.12 h after oral administration of three different commercial tablets.

The apparent Vd/F of acetaminophen ranged from 52.6 to 128 L for subjects receiving the tablet and from 49.4 to 110 L for subjects receiving the solution. The mean apparent volumes of distribution, when corrected by the mean body weight, were 1.2 and 1.02 L/kg, respectively, for the tablet and solution suggesting that acetaminophen distributes into total body water. Divoll *et al.* (27) reported a mean value of 1.09 L/kg after intravenous administration of 650 mg of acetaminophen in young human males. As reported by others, the volume of distribution ranged from 0.60 to 1.36 L/kg (9, 18, 27, 29, 30). The regression-independent bioavailability of the tablet relative to that of the solution was 88.6 ± 13.1%.

In summary, the relative bioavailability of pentazocine and acetaminophen in the capsule-shaped tablet formulation proved to be equivalent to that of the solution. In addition, the pharmacokinetic parameters of pentazocine and acetaminophen were not altered after oral administration of the combination of both drugs.

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