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The calculation of drug absorption rates of morphine sulphate from a sublingual aerosol preparation using quantified maximum entropy

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Abstract

Quantified maximum entropy has been applied to calculate the absorption and disposition kinetics of a sublingual morphine suspension aerosol. The absolute bioavailability, established using an intravenous injection as weighing function, is similar to that reported in the literature for oral morphine preparations. The morphine administered sublingual was only partly absorbed from the oral mucosa, guaranteeing absorption without first-pass metabolism. A large proportion of drug was absorbed from the gastrointestinal tract due to swallowing the preparation. The disposition kinetics of morphine could be established based on its return rate constants from different tissues of the body. In general the drug is distributed into the lipophilic cells of the central nervous system and the body fat simultaneously, but the amount of drug distributed into these tissues depends on the body weight of the volunteers.

Keywords: Absorption rate; Aerosol; Disposition kinetics; Morphine sulphate; Quantified maximum entropy; Sublingual application

1. Introduction

In an earlier paper Podczeck et al. (1995) have used quantified maximum entropy (Charter and Gull, 1987; Charter and Gull, 1991; Charter, 1992) to calculate the absorption rate function of theophylline from sustained release pellet formulations. The quantified maximum entropy approach allows the reconstruction of the disposition kinetics of the drug into tissues, fluids and fat using a spectrum of a theoretically unlimited number of return rate constants. Watson et al. (1996) investigated the possible use of a morphine sulphate suspension aerosol in terms of avoiding the gastrointestinal route of application. The classical data treatment applied by these au-

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thors to investigate the blood level data did not allow the determination of the site of absorption of the drug. Based on a change of metabolite pattern from a comparison with literature data obtained using the oral route of application, the authors concluded that there were pharmacokinetic differences between the sublingual formulation tested and the oral route. However, a change in metabolite pattern will already occur if the drug has only partially been absorbed from the oral mucosa in addition to an absorption in the gastrointestinal tract. Thus, the aim of this analysis was to quantify the relative amount of morphine absorbed from the oral mucosa and the gastrointestinal tract. In this respect, quantified maximum entropy has been applied. Additionally, the analysis of Watson's data allows the estimation of the absolute bioavailability of the drug from the aerosol and the calculation of the disposition kinetics.

Morphine undergoes an excessive pre-systemic clearance by the liver and the intestine (Walsh, 1984), where it will be metabolised mainly into glucuronides (Poulain et al., 1988). This has led in the past to controversy about other than parenteral applications of morphine. Looking at an oral morphine application, a dose of 6–8 times that of the parenteral route will be needed for a similar analgesic effect (Houde et al., 1965). In the case of one single oral administration, the dose required is less than in a continuous treatment of pain (Hanks, 1991).

Although the absolute bioavailability of oral morphine is only between 10 and 43% (Gourlay et al., 1986), where mostly values of about 20% are reported (Vater et al., 1984; Hoskin et al., 1989; Kaiko et al., 1990), the oral route is regarded to be preferable as long as the patient tolerates the treatment (Walsh, 1985), e.g., absence of nausea, tracheal or gastric cancer. The absolute bioavailability is largely influenced by an intrapatient variability, which was reported to contribute to the total bioavailability between 32 and 54% for fasted and fed studies, respectively (Gourlay et al., 1991).

There are cases, where neither the oral nor the parenteral route of morphine application can be followed, and therefore other ways of application have been investigated such as rectal solutions (Moolenaar et al., 1985), suppositories (Lipman and Anderson, 1984; Moolenaar et al., 1988), topical application (Matsuzawa et al., 1994) and buccal tablets (Hoskin et al., 1989). Hence it appeared reasonable that Watson et al. (1996) should test a sublingual suspension aerosol. A sublingual administration of morphine should avoid the deactivation of the drug by the first-pass metabolism (Pfeifer and Borchert, 1980), but from a study on buccal tablets (Hoskin et al., 1989) it is known, that also here the absolute bioavailability of the drug is similar to the oral route, probably because a lot of the drug substance will be swallowed rather than absorbed through the oral mucosa. The use of any kind of solution instead of a tablet formulation allows a more flexible adjustment of the dose to the patient situation (Walsh, 1984), i.e., control of pain without overdosing because of fixed dose levels. In terms of a sublingual application of morphine, such a solution must be administered drop by drop (Hirsch, 1984), which appears rather complicated. Hence, the use of an aerosol could improve the patient's compliance to the sublingual route.

Despite the large enzymatic metabolism, morphine obeys a linear pharmacokinetics (Walsh et al., 1986; Thirlwell et al., 1989). There are, however, different opinions about its disposition. At one extreme a report, that morphine follows a single compartment model (Barrett et al., 1991), exists. This is surprising, since its chemical structure points to an affinity for lipophilic tissues. Two (Moore et al., 1984; Olkkola et al., 1988) and three compartment models (Dahlström et al., 1979; Nahata et al., 1985) are more reasonable. However, the division into compartments is artificial and neglects the interactions between all fluids and tissues in the body. Therefore, the application of quantified maximum entropy could provide a more physiological explanation of the distribution of morphine in the whole body, since it does reconstruct the disposition of the drug from a possible spectrum of return rate constants (Charter, 1992).

Table 1
Morphine blood level (concentration, ng ml^{-1}) after intravenous injection (Watson, 1993)

Time (min)	Volunteer (dose, mg)				
	1 (4.5)	2 (4.0)	3 (4.0)	4 (5.0)	5 (4.0)
5	51.41	78.31		42.62	71.05
10	22.62	31.91	39.65	21.56	24.36
15	18.54	19.38	15.86	16.05	20.43
30	12.71	12.99		10.28	15.48
35			8.54		
45	9.91	9.40	7.32	7.90	10.91
60	7.34	7.19	6.25	7.86	8.88
90	6.65	6.03	4.27	5.52	8.46
120	5.01	4.95	3.36	5.39	6.85
150	5.25	4.64	2.90	4.26	5.33
180	4.78	3.13	2.90	3.64	5.46
210	3.50	2.67	1.98	2.88	4.57
240		2.48	1.83	2.51	4.31
250	1.98				
300		1.86		1.76	4.57
305	1.52				
340			1.22		
365				1.25	
375	1.17				
480				1.25	
600				1.25	

Table 2
Morphine blood level (concentration, ng ml^{-1}) after sublingual administration (Watson, 1993)

Time (min)	Volunteer (dose, mg)				
	1 (9.6)	2 (9.6)	3 (9.6)	4 (9.6)	5 (9.6)
5		2.31			
10			1.43		
15	1.19		3.47	2.95	4.36
30	6.65	6.61	9.17	4.43	8.03
45	6.65	7.27	9.49	7.67	10.12
60	11.28	6.76	7.95	6.20	9.25
90	5.93	4.31	5.84	4.28	9.25
120	3.68	3.00	6.61	4.28	6.11
150	2.97	2.58	4.51	3.69	3.84
180	1.42	2.31	3.95	3.54	2.09
210		1.32	2.47	4.13	2.09
240		1.32	2.64	2.36	
295					1.22
300			1.98	1.77	
360			1.98	1.48	
480				1.48	
600				1.48	
720				1.33	

2. Materials and methods

A pharmacokinetic analysis focusing on the absorption of morphine sulphate based on blood levels reported in a study undertaken by Watson (1993) has been performed using the quantified maximum entropy approach. The important details taken from his study are the following.

(1) The study was approved by the City and Hackney District Health Authority Ethical Committee, London.

(2) There were five healthy volunteers, one male and four female, with an average age of 25.8 years (23–29) and a mean body weight of 58.8 kg (49.0–78.5).

(3) Two preparations were administered randomly to overnight fasted volunteers with controlled fluid intake. The first preparation was an intravenous bolus injection of morphine sulphate dissolved in 0.9% sodium chloride to provide a dose of 0.075 mg kg^{-1} body weight. The second preparation was a morphine sulphate aerosol formulation administered sublingually to provide a dose of 9.6 mg drug. There was a wash-out period of at least 7 days between dose administration.

(4) The morphine plasma levels were determined by the method described by Joel et al. (1988) which is not disturbed by the metabolites morphine-3- and morphine-6-glucuronide.

The calculation of the pharmacokinetic parameters was carried out using the MADAME program (Charter, 1993). Mathematical details of the quantified maximum entropy approach used are available in Podczeck et al. (1995). The ICF-step width optimum was 0.4 (volunteer 3), 0.5 (volunteer 4), 0.6 (volunteer 1) and 0.7 (volunteers 2 and 5).

3. Results and discussion

Watson et al. (1996) followed the morphine blood concentration level over a time period of 12 h. The sensitivity of the assay allows a concentration of 1 ng ml^{-1} and more morphine to be accurately detected (Joel et al., 1988), but concentrations below this threshold level are uncertain and have therefore not been included into the mathematical analysis. Tables 1 and 2 list the relevant morphine blood concentrations for the intravenous and sublingual test, respectively (taken from Watson, 1993). There was no value above 1 ng ml^{-1} in the intravenous study after 10 h. The peak concentrations for the sublingual morphine administration are comparable with those reported for an oral solution (Hoskin et al., 1989) of similar dose.

In all five cases quantified maximum entropy could be successfully applied to model the absorption, distribution and elimination of morphine in

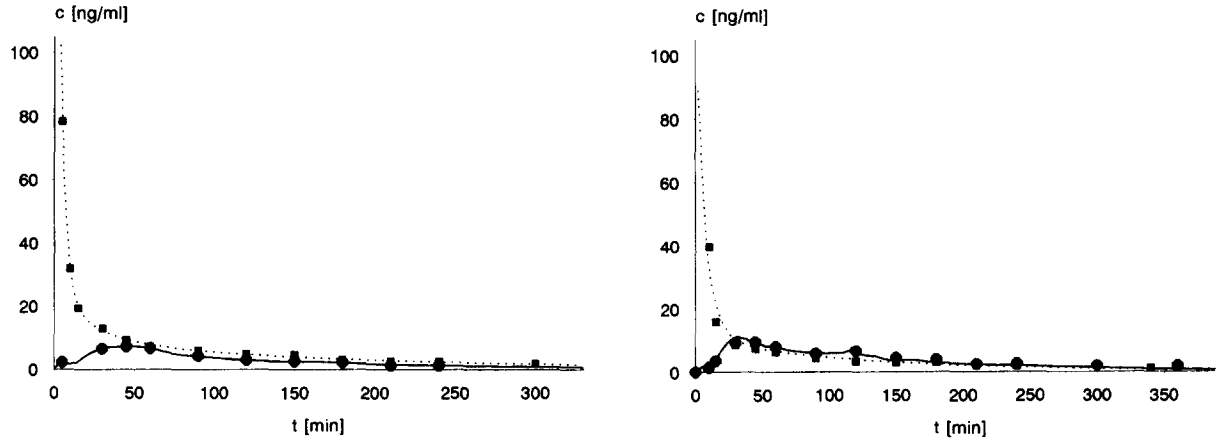

Fig. 1. Comparison between experimental morphine concentrations (i.v., ■; s.l., ●) and model concentrations (i.v., – – –; s.l., ——). (a) Volunteer 2; (b) volunteer 3.

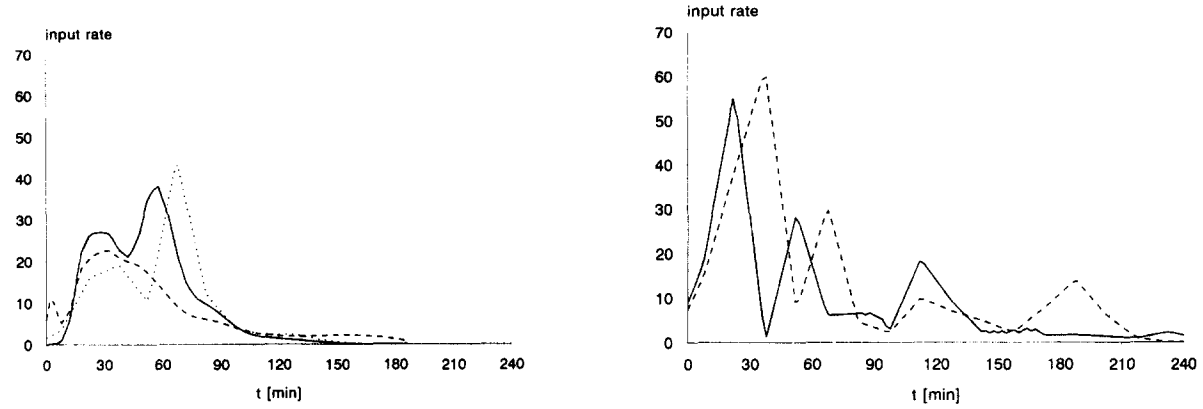

Fig. 2. Sublingual absorption of morphine from an aerosol preparation (a), volunteers 1 (——), 2 (– – –) and 5 (- - -); (b) volunteers 3 (——) and 4 (– – –).

man. The calculated model functions are in good agreement with the measured blood concentrations, and Fig. 1 shows these model functions for two volunteers as an example.

Fig. 2 compares the absorption rate profiles reconstructed for the sublingual administration of morphine in the first 240 min. Volunteer 2 shows only one, broad absorption peak with an absorption end point of about 90 min. Volunteers 1 and 5, however, have clearly 2 absorption peaks, which are separated from each other by about 30 min. The only reason for this could be swallowing of large amounts of the dose administered. Morphine has to be transported into the small intestine to find ideal pH-conditions to be absorbed because of its pK_a (7.8), and this could result in the gap between the two absorption peaks. Finally volunteers 3 and 4 show one large absorption peak and up to three smaller peaks, and the first two peaks are close together. Since the volunteers had already been fasting for 8 h, these particular volunteers could belong to the group of people with a more neutral pH in the empty stomach providing absorption conditions for morphine (second peak), which later for unknown reasons changed, so that a further amount of drug was absorbed from the small intestine (consecutive peaks).

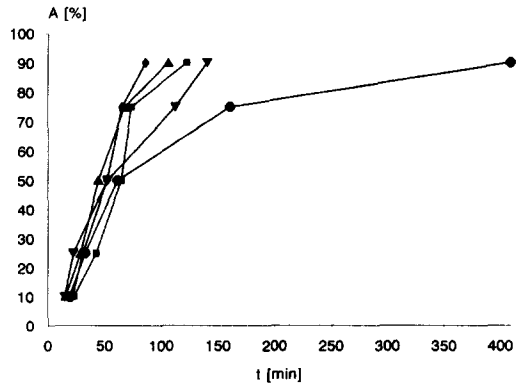

Fig. 3. Cumulative absorption of morphine from a sublingual aerosol preparation. (A) Cumulative absorption; ◆, volunteer 1; ▲, volunteer 2; ▼, volunteer 3; ●, volunteer 4; ■, volunteer 5.

Fig. 3 and Table 3 show the cumulative absorption rate profiles. In most cases the absorption has completed after about 2 h. Only volunteer 4 provides absorption over nearly 7 h. It is interesting to note that volunteer 4 is the only male volunteer in the test.

Table 3 also lists the mean absorption time (MAT) for morphine administered sublingually as a suspension aerosol. Quantified maximum entropy allows the estimation of the intraindividual variability of parameters such as the MAT, and from Table 4 and Fig. 4 it can be seen, that the female volunteers show only little intraindividual

Table 3
Cumulative absorption times of morphine from sublingual application and mean absorption time (MAT)

Volunteer	10% (min)	25% (min)	50% (min)	75% (min)	90% (min)	MAT (min)	IQR (min)
1	21.9	31.1	52.2	65.7	86.1	52.0	47.0–56.3
2	15.8	28.9	44.6	67.7	106.2	53.3	46.9–60.5
3	15.0	22.4	52.5	112.7	140.6	74.9	53.5–90.9
4	19.4	32.8	61.5	161.0	408.9	140.4	103.1–180.4
5	23.1	42.6	64.6	73.7	122.7	66.2	50.4–85.5

Results presented as median values based on Monte Carlo treatment of the posterior distributions. IQR, interquartile range.

and interindividual variability, whereas the male volunteer 4 appears to be very variable in terms of the morphine absorption. There is no clear peak for this volunteer (see Fig. 4), demonstrating a higher level of uncertainty in the data.

The disposition of a drug substance can be characterized by its return rate constants from any body tissue back into the central compartment. Quantified maximum entropy does reconstruct distributions of the return rate constants for drug substances, which are not only distributed in the central compartment. Fig. 5 shows these distributions for all volunteers. The return rate constants vary between 0.001 min^{-1} (very slow return rate from deep tissues and bones) and 1.000 min^{-1} (extremely quick return form body water). The disposition profiles of volunteers 1, 2 and 5 are characterized by a large peak in the range between 0.01 and 0.1 min^{-1} for the return rate constants. The width of the peaks indicates

Table 4
Mean absorption time distributions for single volunteers based on Monte Carlo statistics

Time (min)	Volunteer				
	1 (H, %)	2 (H, %)	3 (H, %)	4 (H, %)	5 (H, %)
<20			6.0	7.0	
<30			4.0		
<40	7.7	3.0	4.0	2.0	
<50	46.2	29.0	7.0		15.4
<60	30.8	41.0	14.0	2.0	23.1
<70	15.4	19.0	9.0	3.0	30.8
<80		6.0	15.0	1.0	15.4
<90		2.0	16.0	4.0	15.4
<100			10.0	6.0	
<110			9.0	2.0	
<120			5.0	8.0	
<130			1.0	8.0	
<140				6.0	
<150				8.0	
<160				10.0	
<170				6.0	
<180				2.0	
<190				4.0	
>190–<230				21.0	

H, relative probability.

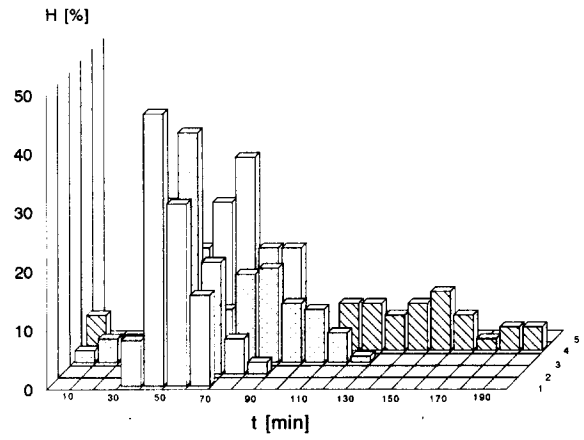

Fig. 4. Mean absorption time distribution of single volunteers (see also Table 3). H, relative probability; t, time.

the distribution of the drug into the lipophilic cell structures of the central nervous system and the body fat simultaneously. The height of the peaks, which decreases in the order: volunteer 1 (g $\ln(k) \approx 15$), volunteer 2 (g $\ln(k) \approx 13$) and volunteer 5 (g $\ln(k) \approx 9$), correlates with the body weight (62.8, 53.5 and 50.0 kg for volunteers 1, 2 and 5, respectively) and may be due to different amounts of body fat. Volunteer 3 (body weight 49.0 kg) provides a very high peak, whereas volunteer 4 (body weight 78.5 kg) shows an extremely broad peak, comparable in height to those peaks of volunteers 1, 2 and 5. The distinctive width could be due to the large body weight of volunteer 4, but there is no obvious reason for the outstanding peak height provided by volunteer 3.

Table 5 lists common pharmacokinetic parameters, based on the posterior distribution functions calculated with quantified maximum entropy. The clearance rate is comparatively low, because Sawe et al. (1981) report a clearance rate range from 5.0 to 16.1 ml min^{-1}. However, quantified maximum entropy splits the distribution volume of the drug in the body into that of the sampling compartment (V_p) and that in the steady-state (V_{ss}), and the calculation of the clearance rate is based on V_p, whereas commonly used software (Johnston and Woollard, 1983) does not distinguish between these volumes providing only a V_{ss}-value. The 'distribution volume' used for the calculations by Sawe et al. (1981) was V_{ss}, which is in the case of morphine about 10 times the value of V_p.

Comparing the clearance rate, which should be the preferred value, with the elimination constant k_{el} (see Table 5), it becomes obvious how misleading the k_{el} is. For example, volunteer 4 has the smallest value of k_{el} implicating a very slow elimination of the drug, but his heavy body and the large V_p cause the drug substance to be spread

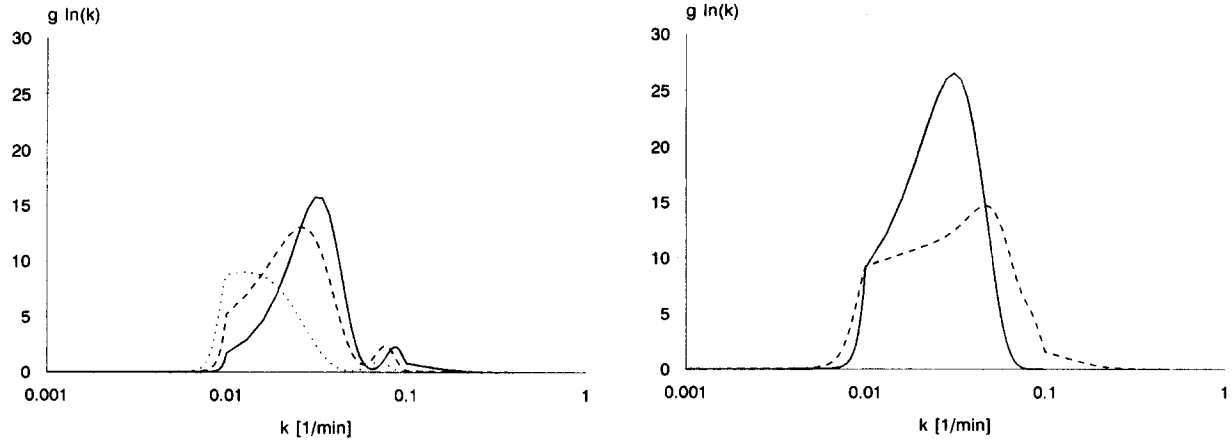

Fig. 5. Disposition of morphine in the human body. (a) Volunteers 1 (——), 2 (– – –) and 5 (- - -); (b) volunteers 3 (——) and 4 (– – –); k, return rate constant.

Table 5
Pharmacokinetic constants and bioavailability of morphine administered as sublingual aerosol

Volunteer	Cl (ml min^{-1})	k_{el} (min^{-1})	V_p (l)	V_{ss} (l)	F	k_a (min^{-1})
1	1.52 (1.37–1.57)	0.18	8.4 (5.9–16.4)	165.9 (131.3–204.9)	0.193	0.01
2	1.37 (1.31–1.45)	0.10	14.2 (13.0–15.6)	159.2 (130.5–190.9)	0.154	0.02
3	1.93 (1.72–2.22)	0.05	36.9 (26.0–47.6)	151.1 (126.5–213.0)	0.273	0.01
4	2.07 (1.90–2.22)	0.04	55.1 (47.1–63.3)	375.5 (288.5–485.1)	0.393	0.01
5	0.76 (0.66–0.88)	0.30	2.5 (0.9–5.4)	58.7 (51.9–135.4)	0.154	0.01

Results presented as median values and interquartile range, based on Monte Carlo treatment of the posterior distributions. Cl, clearance; k_{el}, elimination constant; V_p, volume of the sampling compartment (blood); V_{ss}, distribution volume in steady-state; k_a, absorption constant; F, absolute bioavailability.

over a comparatively large body area which needs to be 'cleaned from drug', and the clearance rate shows that the drug is eliminated from the body more quickly as, for example, in the case of volunteer 1, who has a larger k_{el}. The opposite can be seen if volunteer 5 is compared with the other volunteers. Hence the clearance rate is the only value that adequately describes the elimination of a substance.

Table 5 also lists the absolute bioavailability of morphine administered by the sublingual route. It varies between 15 and 40%, and on average it is within 23.3 $\pm$ 10.2% similarity to the bioavailability of oral morphine preparations, again indicating that a large amount of the dose administered has probably not been absorbed from the oral mucosa, but from the gastrointestinal tract.

In summary, the application of a morphine suspension aerosol appears to be another alternative way of administering morphine, which could be the route of choice in the pain treatment of children or patients with intolerance to the oral route. Quantified maximum entropy was able to establish the absorption and disposition kinetics of such a preparation, providing evidence to the fact that most of the drug substance was absorbed from the gastrointestinal tract instead of the oral mucosa due to swallowing of the preparation. It also showed, that morphine was distributed in the lipophilic cell structures of the central nervous system and the body fat simultaneously in all cases, but it was not possible to separate two disposition peaks from each other implying a rapid exchange of drug between the tissues. Hence both the literature reports of two and three compartment models are reasonable, but the two compartment model reflects the physiological properties of the morphine disposition much better.

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