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LETTER TO THE EDITORS

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Can similar oral blood exposures between studies result in a different bioavailability?

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Vinorelbine is a vinca-alkaloid that was discovered and synthetized in the 1980s by Prof. P. Potier at Centre National de la Recherche Scientifique (Gifs/Yvette, France) [10]. Initially developed and marketed by Pierre Fabre Médicament (PFM, Boulogne, France) as an i.v. form (NAVELBINE® IV) in non-small cell lung cancer (NSCLC) and advanced breast cancer (ABC), an oral form was later developed and marketed. Both forms were licensed to GSK for USA and Canada registration.

As a result, a contractual relationship between both companies existed in order to share all clinical data, including those of the study recently published by Lush [8]. His paper describes an interesting situation that enables one to investigate why different pharmacokinetic parameters may be obtained from apparently similar studies. The aim of this letter is to further discuss the putative causes leading to a discrepancy in bioavailability values between the studies by Marty et al. [9], Rowinsky et al. [11] and Lush et al. [8].

Getting different results from apparently comparable studies is a very common situation in clinical trials. Regarding pharmacokinetic studies, major sources of discrepancies in results may be due to the differences in the selected population, the sampling schedule, the bioanalysis method, or the algorithm used for parameter calculations. Therefore, considerable efforts to set up standardized and reliable conditions have been made right from the early development of vinorelbine in order to collect consistent data for NDA submission.

As the first step, a reference bioanalytical method was defined for use during the entire pharmacokinetic development. It consisted of a HPLC method derived from that published by Jehl et al. [6], but was adapted to blood instead of plasma [12]. Because vinorelbine is mostly bound to platelets (78%) [13], concentrations in blood are higher than those in plasma. As a consequence, measuring vinorelbine in blood enables a longer detection time and a better measurement accuracy for low concentrations. Furthermore, the vinorelbine binding to platelets was demonstrated to be reversible and influenced by the sample temperature [1]. A new equilibrium is rapidly achieved if environmental conditions vary. Therefore, the experimental conditions used for the processing from the blood collection up to the plasma freezing may have a real impact on the concentration levels measured in plasma.

The low absolute bioavailability of oral vinorelbine and its large variability reported by Rowinski et al. [11] are probably explained at first by the administration of an intermediate oral formulation, which was later improved, but also by the measurement of vinorelbine in plasma.

When comparing studies by Marty et al. [9] versus Lush et al. [8], it is observed that the patient inclusion/exclusion criteria were very similar in both the studies and, therefore, the characteristics of the evaluable patients were very close (see Table 1, Fig. 1). Both studies analysed the vinorelbine concentrations in blood. Pharmacokinetic parameters were calculated through a model-independent approach. Two different bioanalytical methods were used: HPLC–UV and LC–MS/MS. However, they were both developed at PFM [12, 13] and successfully cross-validated in order to enable a reliable comparison of results amongst studies (see Table 2). The LC–MS/MS does not produce more accurate values in the usual vinorelbine concentration range but it enables a measurement over a longer period of blood sampling [14]. Thus, the LC–MS/MS method obviously offers an advantage to quantify concentrations over a 168-h period of time.

However, since concentrations in blood over the first 72 h were easily quantifiable by both bioanalytical methods, the advantage of the LC–MS/MS should have mainly concerned concentrations measured after 72 h. Thus, when comparing the two studies over the first 72-h time period, the advantage of the LC–MS/MS over the HPLC is expected to be minor.

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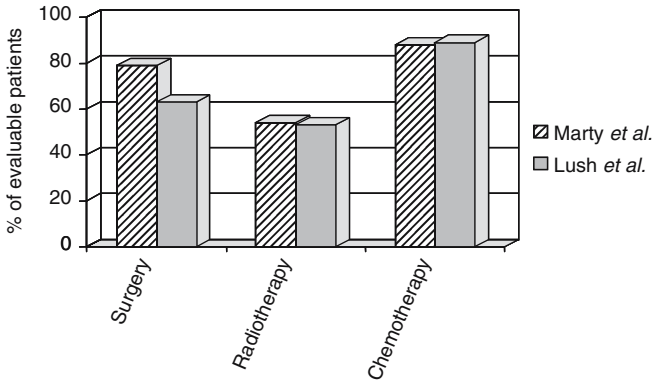

Fig. 1 Comparison of patients' prior treatments (evaluable patients)

Table 1 Comparison of patients

Marty et al. [9]	Lush et al. [8]
32 patients included	29 patients included
24 evaluable patients[a]	19 evaluable patients[a]
4 early vomiting (≤3 h)	5 early vomiting (≤3 h)
4 not evaluable for other reasons	5 not evaluable for other reasons
18 males/6 females	12 males/7 females
Age = 56±12 years [31–73]	Age = 57±9 years [40–73]
BSA = 1.76±0.23 m^2	BSA = 1.95±0.18 m^2
12 liver metastasis/ 24 patients	6 liver metastasis/ 16 patients (3 unknown)
Actual dose	Actual dose
i.v. = 24.9±1.0 mg/m^2	i.v. = 29.5±1.2 mg/m^2
oral = 79.2±3.4 mg/m^2	oral = 66.9±2.1 mg/m^2

[a] Patients without vomiting

The vinorelbine dose levels used in the two studies slightly differed: 80 mg/m² oral versus 25 mg/m² i.v. were used by Marty et al. while 70 mg/m² oral versus 30 mg/m² i.v. were used by Lush et al. Since a dose-proportional increase of exposures was demonstrated for both oral and i.v. vinorelbine [1, 7, 15], blood concentrations may be extrapolated from one dose level to another by arithmetic calculation [9]. To allow direct exposure comparison between the two studies, concentration data collected at 25 mg/m² i.v. and 80 mg/m² oral in Marty's study were dose-adjusted to 30 mg/m² i.v. and 70 mg/m² oral used in Lush's study. On the dose-adjusted AUCs, the same discrepancy between the two studies is observed when using either partial AUCs over 0–72 h or total AUCs calculated on 0–∞ time interval (see Tables 3, 4).

Collection of blood over 168 h and sample analysis with LC–MS/MS allow a better estimate of half-life elimination as discussed by Lush et al. [8]. Nevertheless, the late part of the AUC corresponding to the elimination phase is not the origin of that discrepancy between the two studies. The AUC extrapolations between 72 h and infinity were moderate in both Marty and Lush studies: 15.2 and 13.2% for the i.v. and 11.6 and 11.5% for the oral, respectively. Surprisingly, while the absolute bioavailability of oral vinorelbine differs between studies, comparable oral AUC values on the 0–72 h time interval (1,005±382 vs 940±527 h·ng/ml) as well as similar C_{max} (122±37 vs. 138±66 h ng/ml) were observed for oral vinorelbine (see Table 3).

Conversely for i.v. vinorelbine, discrepancies in both $AUC_{0-72\,h}$ and C_{max} values were observed between the two studies: 1,060±415 versus 1,212±366 h ng/ml, and 914±222 versus 1,887±882 ng/ml, respectively (see Table 4).

As a consequence, the discrepancy between the two studies on the bioavailability of oral vinorelbine is not due to a difference in oral exposures as one might have expected, but to a difference in i.v. exposures. In order to further investigate this lead and to evaluate which part of the curve is more particularly involved, partial AUCs were calculated at various time intervals and compared between studies. Very similar patterns are observed except on the 0–1 h time interval AUC (see Fig. 2). That

Table 2 Comparison between HPLC/UV and LC–MS/MS

	HPLC/UV	LC–MS/MS
Sample preparation	Liquid–liquid extraction	Deproteinisation
Calibration range (ng/ml)	2.5–200	0.25–200
LOQ (ng/ml)	2.5	0.25
Precision in whole blood	CV < 6.9% at LOQ	CV < 11.7% at LOQ
Dilution process	Early samples from i.v. route up to factor 10 in single	Early samples from i.v. route up to factor 20 in duplicate

Retrospective analysis of $n = 164$ clinical samples illustrated a deviation ≤5.8% between the two series of results

Table 3 PK parameters for oral route

Parameter (mean ± SD)	Marty et al. [9]		Lush et al. [8]
Dose (mg/m^2)	80	→70[a]	70
T_{max} (h)	1.4±0.7		1.0±0.6
C_{max} (ng/ml)	133±42	122±37	138±66
$AUC_{0-72\,h}$ (ng/ml)	1,148±436	1,005±382	940±527
AUC_{inf} (h·ng/ml)	1,299±487	1,137±426	1,062±583
F (%) AUC_{last}	43±13		33±18
F (%) AUC_{inf}	40±10		33±18

[a] Dose-adjusted parameters

Table 4 PK parameters for i.v. route

Parameter (mean ± SD)	Marty et al. [9]		Lush et al. [8]
Dose (mg/m^2)	25	→30[a]	30
T_{max} (h)	0.3±0.1		0.3±0.1
C_{max} (ng/ml)	762±185	914±222	1,877±882
$AUC_{0-72\,h}$ (ng/ml)	883±346	1,060±415	1,212±366
AUC_{inf} (h ng/ml)	1,042±392	1,250±470	1,397±380

[a] Dose-adjusted parameters

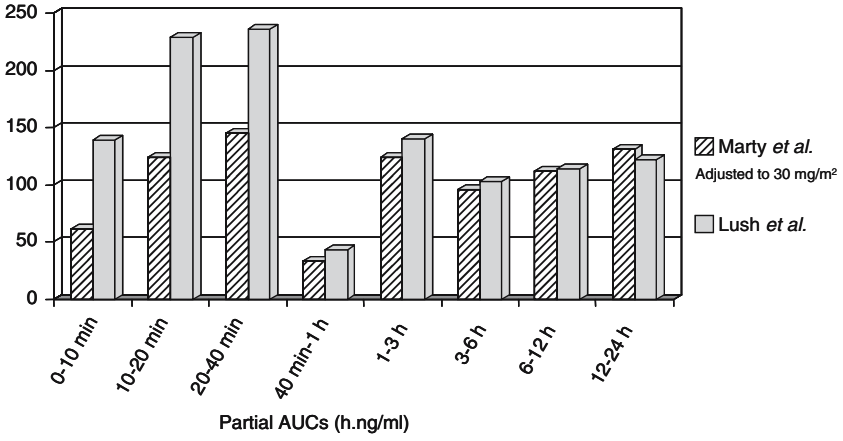

Fig. 2 Mean partial AUCs for i.v. route

fraction of AUC represents 33 and 49% of the global i.v. AUC for Marty and Lush, respectively. As a matter of fact, concentrations achieved at the end of vinorelbine infusion were twice higher in Lush's than in Marty's study: 1,887±882 versus 914±222 ng/ml. Marty's data are more in line with those published by Khayat et al. [7] also collected in blood) than that of Lush (see Fig. 3).

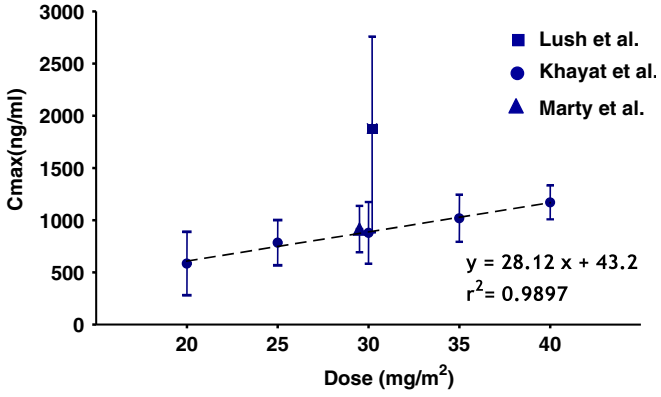

Fig. 3 C_{max} observed at the end of a 20-min infusion of i.v. vinorelbine mean ± SD (ng/ml)

In contrast very similar partial AUCs, whatever the time intervals, were observed for the oral administration (see Fig. 4).

These results illustrated a very unexpected influence of the infusion rate. For a 0.33 h (20 min) infusion planned in the protocol, the duration varies from 0.17–0.42 h producing a 547–4,045 ng/ml C_{max} range in Lush's study while it varies from 0.15–0.50 h producing a 484–1,310 ng/ml dose-adjusted C_{max} range in Marty's study. The reasons for these differences are unclear.

The 10% difference in the absolute bioavailability between studies is considered unlikely to have clinical consequences since other factors may affect the variability [8]. However, when evaluating the vinorelbine oral dose likely to provide similar efficacy/safety to the i.v. therapeutic dose of 30 mg/m², equivalent AUCs will be achieved with about 90 mg/m² instead of about 80 mg/m² oral vinorelbine from bioavailability factors of Lush and Marty's, respectively. From clinical experience, comparable safety and efficacy between 30 mg/m² i.v. and 80 mg/m² oral vinorelbine were observed in NSCLC and ABC [4, 5], whereas 90 mg/m² oral vinorelbine has not been explored but is likely to result in an increased toxicity since it is closer to the 100 mg/m² MTD [2].

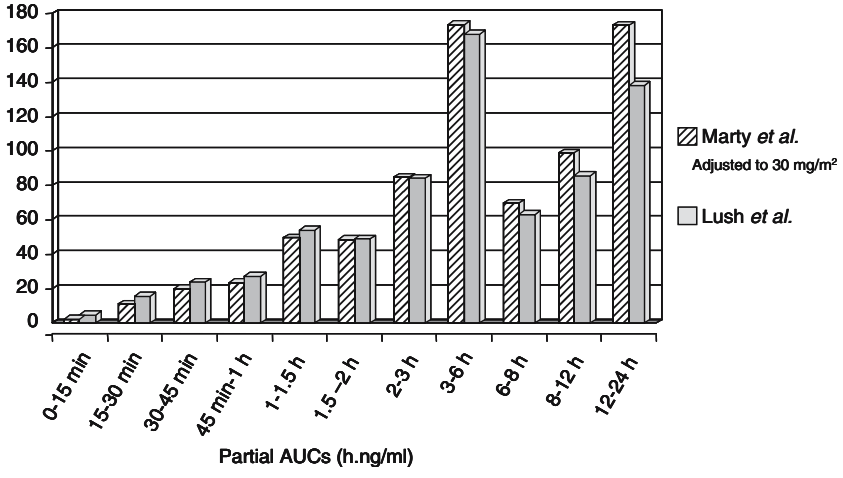

Fig. 4 Mean partial AUCs for oral route

A recent study completed on 48 evaluable patients in a crossover design, 30 mg/m² i.v. and 80 mg/m² oral vinorelbine, confirmed Marty's data [3], and illustrated an equivalent blood AUC between 30 mg/m² i.v. and 80 mg/m² oral.

In conclusion, the discrepancies between the absolute bioavailability values of oral vinorelbine published by Marty et al. [9] and Lush et al. [8] are surprisingly not the consequence of a difference in blood exposures following oral administrations. Whilst the oral exposures were comparable, the i.v. exposures were different and more particularly over the first hour including the 20 min of vinorelbine infusion. In both studies, an electrical syringe driver was used, which is likely to control the infusion rate over these 20 min. quite well. Nevertheless, higher concentrations were observed in one study twice as compared to the other.

This letter illustrates that when performing an absolute bioavailability study, much attention must be paid not only to control the oral administration conditions, as is usually done, but also to control the i.v. administration conditions. If not, an unexpected situation could arise in which we obtain two different bioavailability values for the oral form despite very similar oral exposures.

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