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Dissolution time, on reconstitution, of a new parenteral formulation of doxorubicin (Doxorubicin Rapid Dissolution)

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Over the past 15 years doxorubicin (Adriamycin) has become one of the most effective and widely used antitumour agents (Wiemann and Calabresi, 1985; Garewal et al., 1984; Young et al., 1983; Beijnen et al., 1985.). During this time the formulation used has been a freeze-dried mixture of doxorubicin-HCl and lactose. The recommended diluents, Water for Injections or Sodium Chloride Injection, while generally proving satisfactory have nonetheless from time to time given rise to gel formation during reconstitution with consequent prolongation of dissolution time (Adriamycin Data Sheet, U.K., 1986). Reconstitution with Sodium Chloride Injection seemed, in particular, to be associated with this problem. In addition, the prolongation of dissolution time is inevitably linked with an increase in shaking, and vigour of shaking, which can appreciably increase the risk of leakage of this hazardous agent from the vial.

Recently the laboratories of Farmitalia Carlo Erba have developed a new patented formulation of doxorubicin-HCl for injection involving the use of hydroxybenzoates in sub-preservative concentrations, to enhance the dissolution rate. The new preparation is called Doxorubicin Rapid Dissolution, and is believed to achieve superior dissolution by disruption of hydrogen bonding between anthracycline moieties and possibly, the lactose and water. Pilot studies have demonstrated a marked difference between old and new formulations on reconstitution; with Water for Injection the rate of dissolution was enhanced approximately 5-fold and with Sodium Chloride Injection about 25-fold by the new formulation. The time to complete solution of the contents of a 50 mg vial was reduced to about 30 s regardless of whether the solvent was Water or Sodium Chloride Injection. It was therefore decided to carry out a comparative study involving larger numbers of vials, more than one operator, and according to a randomised double-blind design.

Commercially available Adriamycin vials and the new Doxorubicin Rapid Dissolution product were prepared as identical preparations, indistinguishable by eye, labelled only as required for the study. At each of two centres they were presented as two blocks of 20 vials, one block for reconstitution with Sodium Chloride Injection and the other with Water for Injections. The vials were numbered in accordance with a double-blind randomisation table; the code was sealed and not available to the experimenters until the study had been completed and the results analysed. The randomisation and subsequent analysis were car-

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ried out by the Biostatistics Section of the Medical Department, Farmitalia Carlo Erba Ltd., St. Albans, U.K. In order to limit the influence of the operator the study was carried out in two major centres where cytotoxics are extensively used. Within each block the vials were selected for reconstitution at random and the order was not recorded.

The reconstitution was carried out by a pharmacist or technician taking all the usual precautions required for the preparation of cytotoxic injections including the use of gowns, gloves and masks and laminar flow cabinet.

Each 50 mg vial was reconstituted with 25 ml of solvent.

The timer (APL) started the stopwatch at the moment the needle penetrated the rubber bung since the internal negative pressure draws solvent from the syringe the moment penetration occurs. Steady pressure on the plunger of the syringe ensured that the 25 ml of solvent was delivered in a steady stream over a few seconds.

After addition of the reconstituting solvent the needle was withdrawn and the vial swirled gently without shaking or inversion. If the contents did not dissolve within 30 s more vigorous shaking was permitted, but with care to avoid excessive froth which can make determination of the end-point difficult.

The stopwatch was stopped when both the reconstituting pharmacist and observing timer agreed that no particles remained discernible. The time to dissolution was then entered on the record sheet provided.

The results were clear-cut even though the agitation techniques differed substantially between the two centers, which gave an accurate reflection of the variation encountered in general usage of such products. In Belfast a steady rate of agitation was maintained, as in the pilot study, irrespective of the initial rate of dissolution while at the Marsden slow initial dissolution prompted more energetic agitation with a consequent shortening of the residual dissolution time.

The results have been analysed in an exploratory fashion by plotting and examining listings of the dissolution times, ranked and classified by formulation (Adriamycin or Doxorubicin Rapid Dissolution) within each centre-solvent block. Summary means were also calculated, with corresponding confidence limits and, with estimates for the difference between formulation means, these data are given in Table 1.

Formal analysis of variance was not possible because of gross differences between the different blocks in the variability of times about these means. Within each block, the variability of the observations differed significantly between the two formulations and hence the standard error calculated for the difference between the two formulation means is approximate.

It is clear that consistently lower dissolution times were observed with the Doxorubicin Rapid Dissolution formulation than with the original product. With both solvents, in each centre, it is also clear that the variability in the dissolution times was substantially less with the Rapid Dissolution formulation. These observations are most efficiently summarised by the confidence intervals given in Table 1 for the mean dissolution time of each formulation related to solvent and centre.

Because there is so little overlap in the distributions of the dissolution times for the two formulations, more formal statistical comparison is not strictly necessary. It may, however, be noted that in each block the difference between formulation means may be compared by relating the difference in mean dissolution time to the approximate standard error. A significance level for the difference between formulations may also be derived from a Mann-Whitney *U*-test (Siegel, 1956) of the differences between the distribution of dissolution times as follows:

London	Water as solvent	$P < 0.002$
	Saline as solvent	$P = 0.00002$
Belfast	Water as solvent	$P = 0.00001$
	Saline as solvent	$P = 0.00001$

It is evident from the results of this study that the very small formulation change involved has resulted in a major improvement in ease of reconstitution of doxorubicin hydrochloride injection. This example of formulation development is an indication of the way in which even products of long-standing and wide usage may be markedly

TABLE 1

Summary data classified by centre, solvent and formulation

Centre:	London				Belfast			
Solvent:	Water		Saline		Water		Saline	
Formulation:	Adria	Rapid	Adria	Rapid	Adria	Rapid	Adria	Rapid
Time (min)								
< 1	3	10		9	4	10		2
1–2	6		3	1	6			6
2–3	1		4					2
3–4			2					
4–5			1					
5–15							10	
Mean (s)	72	31	148	37	66	21	665	89
95% confidence limits	49	28	115	28	55	19	588	65
	96	34	181	45	77	23	743	113
Difference								
Mean (s)	41		111		45		577	
Approx. S.E.	12		17		6		41	

Adria = Adriamycin; Rapid = Doxorubicin Rapid Dissolution.

improved sometimes as in this case, quite dramatically, by quite small changes in composition.

It is anticipated that, given the widespread use of this important antitumour agent, the new formulation of doxorubicin will result in a considerable saving of time and a reduction in the hazards of operator exposure.

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