

ADVERSE REACTIONS TO DEXTRAN IN SWEDEN 1970–1979

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Abstract. In a retrospective investigation of the period 1970–1979, 478 reports on cases of dextran-induced anaphylactoid/anaphylactic reactions (DIAR) were found. In 458 of these dextran was judged to be the causative agent. The number of units of dextran 40 and 70 used during this decade was 313 598 and 1 051 668, respectively. During the last five years, when reporting of severe adverse drug reactions was mandatory, the incidence of severe DIAR per unit administered was 0.015% for dextran 40 and 0.025% for dextran 70. The incidence of fatal DIAR was 0.003% and 0.004%, respectively. We found a male:female ratio of 1.5:1 for all DIAR while for the most severe DIAR this ratio was 3:1. The mean age of the patients was higher in severe than in mild DIAR. Allergic disease did not predispose for severe DIAR. Diabetes, cardiovascular and pulmonary diseases and chronic inflammation were more frequent among the patients who had suffered the most severe DIAR. 22 reactions were characterized by fever and/or shivering, and in 19 of these cases the reaction occurred after infusion of more than one unit of dextran. Severe DIAR occur after infusion of a few ml of dextran. Fatal DIAR during anaesthesia occurred almost exclusively in patients under spinal or epidural blockade. A favourable outcome of resuscitation in DIAR with cardiac arrest was possibly promoted by the infusion of large amounts of crystalloid fluids. We could not show that therapy with steroids, epinephrine or isoprenaline influenced the outcome. Fatal DIAR occurred even after infusion of only 0.5–1 ml of dextran, and we strongly advise against the use of “biological test-doses”.

Dextran is used clinically for plasma volume expansion, improvement of blood flow and thromboprophylaxis. Like other colloid infusion fluids, dextran may elicit rare adverse reactions. The clinical picture of dextran-induced anaphylactoid/anaphylactic reactions (DIAR) ranges from innocuous skin manifestations to circulatory shock, sometimes fatal. In recent years an increase of the number of reported adverse reactions to many drugs,

including plasma substitutes, has been observed, reflecting either a true increase of reactions or an improved reporting by physicians (Fisher, 1975; Furhoff, 1977). The reported incidence of DIAR varies from 0.03 to 4.7% in different studies and that of severe DIAR from 0.008 to 0.25% (Bauer & Ösling, 1970; Schöning & Koch, 1975; Ding & Messmer, 1977; Furhoff, 1977; Gruber et al., 1980).

The aim of the present study was to determine the incidence of severe DIAR based on the number of dextran units used in Sweden over a ten-year period, to elucidate the symptoms of adverse reactions to dextran and to search for characteristic clinical data for patients reacting to dextran.

PATIENTS AND METHODS

Dextran use

The number of dextran units delivered from all hospital pharmacies to clinical departments was kindly supplied by the National Corporation of Pharmacies, a federal institution responsible for all drug distribution in Sweden.

Reports on adverse drug reactions

Case reports on adverse reactions to dextran were collected from: 1) the Section for Adverse Drug Reactions, Department of Drugs, National Board of Health and Welfare; 2) Pharmacia AB, Uppsala, manufacturer of all dextran used in Sweden; and 3) the Swedish Drug Insurance, established 1978. In addition, some cases previously not reported were found at various hospitals during the investigation.

After preliminary evaluation of the completeness of the reports 64 hospitals were contacted with requests for copies of hospital records.

In 426 of the 478 cases copies of complete hospital records or discharge notes were available for the assessment. In the remaining 52 cases the available reports were sufficient for a valid evaluation.

Data were transferred to a proforma which was adapted

Table I. Characteristic symptoms in dextran-induced anaphylactoid/anaphylactic reactions (DIAR) of different grades of severity (modified from Ring, 1978)

Grade of severity	Characteristic symptoms
I	Skin manifestations (flush, erythema, urticaria). Lumbar pain
II	Mild to moderate hypotension (Lowest recorded BP >40–60 mmHg depending on duration). Gastrointestinal disturbances. Respiratory distress
III	Severe hypotension, shock (BP ≤40–60 mmHg). Bronchospasm
IV	Cardiac and/or respiratory arrest
V	Fatal reaction

for computer analysis. The following data were registered for each case report: Dextran preparation used; patients' age and sex; date of suspected adverse reaction; Swedish county; main diagnosis according to chapter in WHO classification (ICD 1966), concomitant diseases and conditions; concomitant long-term medication; earlier infusion of dextran and previous history of adverse reaction to dextran; medical indication for dextran administration; type of anaesthesia during adverse reaction; type of operation during adverse reaction; symptoms of the adverse reaction; volume of dextran given and time elapsed from start of dextran infusion to the first symptoms of adverse reaction; total volume of dextran given; therapeutic measures; complications to therapy; laboratory analyses; clinical course.

Classification and assessment of adverse reactions

Adverse reactions were classified as to type, severity and causal relationship to dextran. Cases with symptoms suggestive of DIAR were divided into grades of severity, Table I. A separate group of reactions characterized by the appearance of fever and/or shivering could be identified. Other reactions with unspecific symptoms were classified as miscellaneous. The causal relationship to dextran was classified as either likely or non-likely. In order to be classified as likely other causes of the reaction should not be evident, and for DIAR grades III–V, if a serum sample drawn before the reaction was available, the titre of dextran-reactive antibodies measured with passive hemagglutination should be elevated (DRA-ph ≥256, Hedin & Richter, 1982).

Statistical analyses

Chi-square test and Fisher's exact test were used for the statistical analyses.

RESULTS

A total of 1 365 266 units of clinical dextran (dextran 70 and 40) were delivered to clinical depart-

ments in Sweden 1970–1979. We found 478 reports on adverse reactions in connection with dextran infusion. 170 cases were reported to the Health authorities alone, 116 cases were reported to Pharmacia AB alone, and 176 cases were reported to both. The annual number of reports are shown in Fig. 1. Five cases were reported to the Swedish Drug Insurance, but only two of these were reported to this institution alone. Fourteen cases were found not previously reported to the institutions mentioned above.

Classification

In 458 of the 478 cases dextran was judged to be probable or possible cause of the reported reaction (Table II) and thus denoted as causal relationship likely. Their allotment to dextran 70 (Macrodex®) or dextran 40 (Rheomacrodex®) for the years 1975–1979 is given in Table III. There were more reactions reported during 1975–1979 (316) than 1970–1974 (149), $p < 0.001$. The incidence of severe DIAR (grades III+IV+V) per unit of dextran administered was 0.008% for the first and 0.022% for the last five years.

In 20 of the 478 cases dextran was not considered to be the causative agent; the causal relationship is therefore denoted as non-likely, Table II. These 20 cases are excluded from the following presentation of results. In the four fatal cases, another cause of death than DIAR was verified at autopsy.

No cases of renal complications were reported.

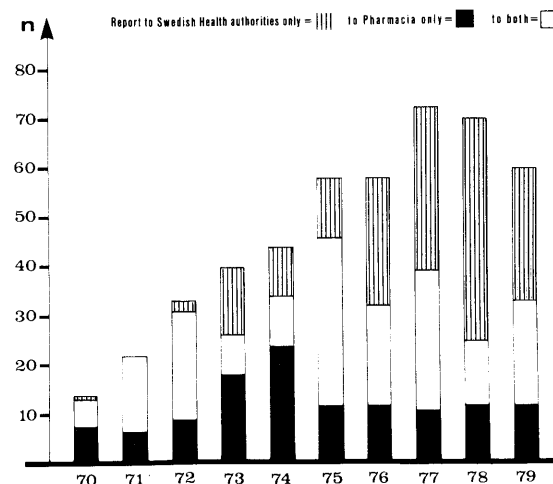


Fig. 1. Adverse reactions to dextran in Sweden 1970–1979. Number of annual reports to Health authorities, manufacturer or both, $n = 462$.

Table II. Adverse reactions to dextran in Sweden 1970–1979. Causal relationship to dextran for different types of reactions and grades of severity

Causal relationship	DIAR, grades of severity					Fever/shivering	Miscellaneous	Total
	I	II	III	IV	V			
Likely	80	152	112	61	28	22	3	458
Non-likely	1	4	1	1	4	4	5	20
Total	81	156	113	62	32	26	8	478

Two cases of haemorrhagic complications were reported, one was classified as non-likely.

Geographical distribution

The number of reports from different counties in Sweden were closely related to sales figures in the corresponding areas.

Clustering

Occasional clustering of adverse reactions at certain hospitals or during a certain short time period occurred several times during the investigation period. We found no seasonal variation apart from a low incidence during vacation time in summer. A few doctors were responsible for a comparatively large number of reports, irrespective of where in the country they were working at the moment.

Sex and age

A sex difference was found with a male–female ratio of 1.5:1. For the most severe reactions (grades IV+V) this ratio was 3:1, $p<0.001$, Fig. 2. The mean age of the dextran reactors was found to be higher the more severe the reaction had been, $p<0.001$, as shown in Fig. 2.

Main diagnosis

The main diagnoses were non-malignant gastrointestinal diseases in 84 cases, various types of injuries in 79, genitourinary diseases in 71, cardiovascular diseases in 62, musculoskeletal diseases in 51, neoplastic diseases in 51, obstetric conditions in 19 and various other disorders in the remaining 41 cases. DIAR of different grades of severity were evenly distributed in the various diagnostic groups, except that all six patients with diabetes as main diagnosis suffered severe reactions, $p<0.02$.

Concomitant diseases

The major concomitant diseases noted are shown in Table IV. A higher incidence of cardiovascular disease ($p<0.01$), pulmonary disease ($p<0.05$) and chronic inflammation ($p<0.05$) was found among patients who had suffered cardiac arrest or fatal reactions (grades IV+V) than among patients who had only had mild reactions (grades I+II). Liver cirrhosis, drug allergy and diabetes, when found as a concomitant disease, were evenly distributed among these groups. A history of allergic disease including bronchial asthma was present more often in patients with mild DIAR (grades I+II) than in patients with reactions of grades IV+V, $p<0.05$.

Table III. Adverse reactions to dextran in Sweden 1975–1979 (causal relationship likely). Types of reaction and grades of severity in relation to dextran preparations

Incidence (%) within brackets

Dextran prep.	No. of units	DIAR, grades of severity					Fever/shivering	Miscellaneous	Total
		I	II	III	IV	V			
Dx 70	488 748	51	82	69	37	18	6	0	263
				124 (0.025)					
Dx 40	159 008	10	12	9	7	5	8	2	53
				21 (0.013)					
Total	647 756	61	94	78	44	23	14	2	316
				145 (0.022)					

Table IV. Adverse reactions to dextran in Sweden 1970–1979. Types of reaction and grades of severity in relation to concomitant diseases

	DIAR, grades of severity					Fever/ shivering	Miscella- neous	Total
	I	II	III	IV	V			
Cardiovascular disease	18	51	33	22	20	4	2	150
Diabetes	3	5	4	5	3	0	1	21
Pulmonary disease	2	8	4	7	4	0	0	25
Liver cirrhosis	1	2	1	0	1	0	0	5
Chronic inflammation	18	47	33	21	15	4	0	138
Allergic disease	8	16	13	2	1	1	0	41
Drug allergy	5	7	12	7	0	0	0	31

Concomitant medication

An average of 2.2 drugs per patient was taken by 194 patients, while 172 patients had no concomitant long-term medication. For 92 patients information is lacking.

Previous dextran infusion

Six patients had previously been treated with dextran. One of these possibly experienced a DIAR in connection with the previous infusion also. For 274 cases it could be ascertained that they had previously never been treated with dextran, while for the remaining 178 cases this could not be determined.

Indication for dextran administration

The medical indication for dextran infusion in the 458 patients with DIAR was stated to be thrombo-embolic prophylaxis in 226 cases, blood volume replacement in 133, improvement of microcirculation in 64, and various other specified indications in 12 cases. In 23 cases the indication was not stated. Blood volume replacement was a more frequent indication in severe DIAR (grades III+IV+V) than in mild DIAR (grades I+II), (37 and 25% respectively; $p < 0.05$). No significant difference could be detected between the other indication groups as to the distribution of DIAR of different grades of severity.

Anaesthesia and surgery

The number of DIAR seen during various types of anaesthesia are shown in Table V. DIAR in relation to operation is shown in Table VI. A larger proportion of severe reactions occurred during anaesthesia ($p < 0.001$) and surgery ($p < 0.01$) than in non-anaesthetized and non-operated patients, respectively. Fatal reactions during anaesthesia occurred almost exclusively in patients under epidural or spinal anaesthesia.

The type of surgery performed when DIAR occurred was general surgery in 54 cases, urological procedures in 32, orthopaedic operations in 26, and gynecological or obstetric operations in 17 cases. The five fatal reactions that occurred during operation were all in patients undergoing prostatic surgery. Otherwise the distribution of DIAR of different grades of severity was similar for different types of surgery. In patients under anaesthesia an average number of 3.2 different drugs had been given before DIAR, most of which for the induction of anaesthesia.

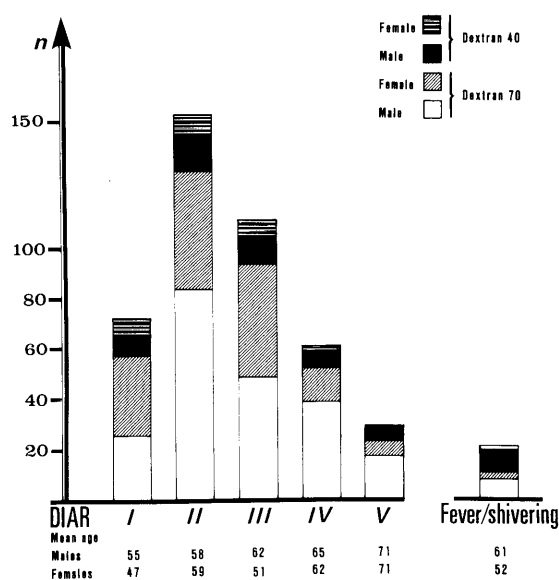


Fig. 2. Adverse reactions to dextran in Sweden 1970–1979, causal relationship likely. Types and grades of severity in relation to dextran preparations, sex and mean age.

Table V. Adverse reactions to dextran in Sweden 1970–1979. Types of reaction and grades of severity in relation to anaesthesia

	DIAR, grades of severity					Fever/ shivering	Miscella- neous	Total
	I	II	III	IV	V			
Epidural or spinal anaesthesia	7	20	24	19	14	0	0	84
Local anaesthesia	2	7	2	1	0	0	0	12
General anaesthesia	18	37	39	25	1	0	1	121
All types of anaesthesia	27	64	65	45	15	0	1	217
No anaesthesia	50	87	42	16	13	21	2	231
Unknown	3	1	5	0	0	1	0	10
Total	80	152	112	61	28	22	3	458

Symptoms

Symptoms of DIAR included allergic skin manifestations (flush, erythema, urticaria, conjunctivitis, Quinckes oedema, pruritus etc.) in 75% of the patients. Respiratory symptoms ranging from slight dyspnoea to severe bronchospasm were observed in 36%, gastrointestinal symptoms (nausea, vomiting) in 23%, and pain in the back or abdomen in 7% of the patients. Circulatory symptoms were observed in 78% of the DIAR reported. In 92% of severe DIAR, symptoms other than circulatory were observed and all fatal DIAR were associated with at least one anaphylactic symptom of the types mentioned above.

Fever and/or shivering were the predominant symptoms in 22 cases, Table II.

Latency

Table VII shows the interval between start of the dextran infusion and the first symptoms of adverse reaction as well as the volume of dextran infused before the first symptoms appeared. The time interval was shorter, $p < 0.02$, and the volume smaller, $p < 0.0002$, with increasing severity of the DIAR. Of the 28 fatal reactions 27 occurred within 5 minutes from the start of the infusion and 25 occurred

when less than 25 ml of dextran had been infused. In three cases a "biological test dose" of only 0.5–1 ml elicited the fatal reaction. The total volume of dextran infused was generally larger than the volume infused before the first symptoms of DIAR because of failure to immediately recognize the cause of the patient's condition.

Nineteen of the 22 reactions characterized by fever/shivering occurred after infusion of more than one unit of dextran.

Therapeutic measures

In 445 of the 458 cases the dextran infusion was stopped as soon as it was felt that the adverse reaction could be related to dextran. In six cases dextran was employed as a blood volume expander in the treatment of the circulatory symptoms, in two cases inadvertently. Other therapeutic measures are shown in Table VIII. When comparing data from grade IV and grade V reactors we found that more of the survivors had been treated with infusion of crystalloid solutions (89 and 68%, respectively, $p < 0.05$). No other significant difference between these two groups as to therapy could be detected.

Table VI. Adverse reactions to dextran in Sweden 1970–1979. Types of reactions and grades of severity in relation to operation

	DIAR, grades of severity					Fever/ shivering	Miscella- neous	Total
	I	II	III	IV	V			
During operation	20	37	41	27	5	0	1	131
Not during operation	57	114	69	34	23	21	2	320
Unknown	3	1	2	0	0	1	0	7
Total	80	152	112	61	28	22	3	458

Table VII. Adverse reaction to dextran in Sweden 1970–1979. Types of reaction and grades of severity in relation to volume infused and time from start of infusion before first symptom of adverse reaction

	DIAR, grades of severity					Fever/ shivering	Miscella- neous	Total
	I	II	III	IV	V			
<i>Volume (ml)</i>								
≤25	43	100	77	46	25	0	0	291
>25; ≤100	20	43	24	10	3	0	0	100
>100; ≤500	11	5	8	2	0	3	2	31
>500	1	0	0	0	0	19	1	21
Unknown	5	4	3	3	0	0	0	15
Total	80	152	112	61	28	22	3	458
<i>Time (min)</i>								
≤5	46	106	85	52	27	0	0	316
>5; ≤10	17	27	23	6	1	0	0	74
>10; ≤60	8	14	1	0	0	1	0	24
>60	4	1	0	0	0	21	3	29
Unknown	5	4	3	3	0	0	0	15
Total	80	152	112	61	28	22	3	458

Immunologic data

Serum samples from 130 patients have been analyzed for dextran reactive antibodies by passive hemagglutination (Hedin & Richter, 1982). In 32 cases analyses of serum samples drawn prior to the reaction were performed. The results are summarized in Fig. 3.

Blood gas analysis

Results from arterial blood gas analysis were available in 69 cases. During severe reactions a pronounced metabolic acidosis was regularly found, even after administration of sodium bicarbonate in

amounts judged as adequate for the patients condition.

Recovery, sequelae

A prolonged hospitalization was stated in 95 cases (postponement of operation, prolonged recovery, complications etc.). The highest frequency was seen in severe non-fatal reactions. Sequelae occurred in 12 cases; myocardial infarction in four, permanent severe brain damage in three and minor brain damage in three cases.

Major complications to therapeutic measures were seen in seven cases. Pneumothorax requiring chest drains following cardiac massage and/or intracardiac injections occurred in six of these.

In the 28 fatal reactions death occurred within two hours in 21 cases, within two to 24 hours in three cases and after more than 24 hour in the remaining four. Autopsy had been performed in 24 cases, and the findings were consistent with fatal DIAR.

DISCUSSION

Incidence

During the decade 1970–1979 the number of annual reports on adverse reactions to *all* drugs to the National Board of Health and Welfare has increased, Fig. 4. Nevertheless, the annual number of reports on deaths associated with drug use has remained on a remarkably constant level. This has been taken to indicate an overall high degree of

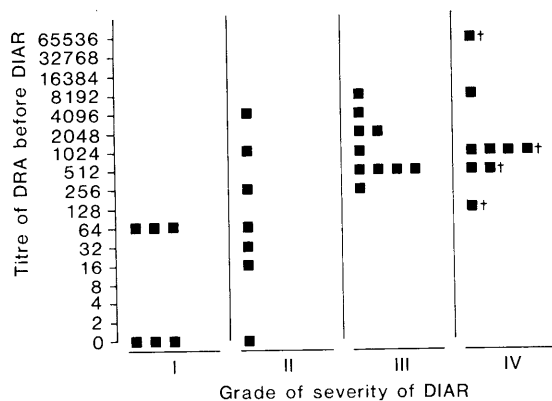


Fig. 3. Titer of dextran reactive antibodies (DRA) measured with passive hemagglutination in serum samples taken before the reaction in patients with DIAR of different grades of severity. $n=32$.

Table VIII. Adverse reactions to dextran in Sweden 1970–1979. Types of reaction and grades of severity in relation to therapeutic measures, pharmacological therapy and fluid therapy

	DIAR, grades of severity					Fever/ shivering	Miscella- neous	Total
	I	II	III	IV	V			
Total number	80	152	112	61	28	22	3	458
<i>Therapeutic measures</i>								
Termination of dextran inf.	78	148	111	60	27	19	2	445
Oxygen	1	40	74	58	22	1	0	196
Controlled ventilation	0	8	38	52	22	0	0	120
Intubation	0	2	14	28	18	0	0	62
Cardiac massage	0	0	0	47	24	0	0	71
Defibrillation	0	0	0	18	12	0	0	30
Intracardiac injection	0	0	0	10	13	0	0	23
<i>Pharmacological therapy</i>								
Epinephrine	4	15	48	34	20	0	0	121
Isoprenaline	0	2	6	16	7	0	0	31
Corticosteroids	17	86	93	41	17	2	0	256
Antihistamines	7	20	24	5	3	0	0	59
Other drugs	14	63	75	44	19	0	1	216
<i>Fluid therapy</i>								
Crystalloid infusion	21	85	97	54	19	1	0	277
Colloid infusion	2	16	36	10	3	0	0	67
Buffer infusion	0	9	22	45	16	0	0	92

reporting of fatal reactions to the authorities in contrast to the underreporting of less serious adverse reactions (Böttiger et al., 1979). Mandatory reporting of fatal and serious adverse reactions was introduced in 1974, which probably accounts for part of the increase in the total number of reports experienced during the last five-year period. The number of annual reports on adverse reactions to dextran has increased in a similar fashion as depicted in Fig. 1.

During the period 1975–1979 the annual number of reports on adverse reactions to dextran has stabilized on a level of 60–70 reports/year. Thus, it seems logical to use this period for estimation of the incidence of severe DIAR. These figures based on number of units, are 0.025% for dextran 70, 0.013% for dextran 40 and 0.022% for both types. These data represent a *minimum*, since some severe reactions may not have been reported and all of the delivered dextran units may not have been used. When comparing these incidence figures with the results of other investigations (Table IX) it must be kept in mind that incidence figures based on *units* of dextran obviously must be lower than incidence figures based on number of *patients*,

since many patients receive two or more units of dextran during a hospital stay.

Prospective studies have shown that mild DIAR are more common than severe ones. In the multicenter trial reported by Gruber et al. (1980), 12 of 22 DIAR were of grade I. The incidence of DIAR with skin symptoms only cannot be assessed from the present investigation both because of probable underreporting and because mild symptoms might have escaped detection i.e. during anaesthesia and surgery. On the other hand it is quite clear that

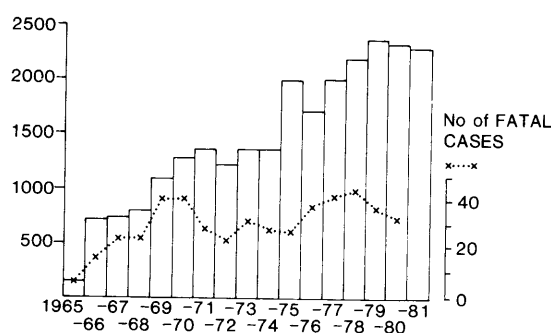


Fig. 4. Swedish Adverse Drug Reaction Committee: number of annual reports of adverse reactions to *all* drugs and number of reports on fatal cases.

Table IX. Incidence of severe DIAR (grade $\geq$ III) in different studies

	Pro/retro- spective study	Dextran prepara- tion	n	Incidence (%)
<i>Calculations per patient</i>				
Gruber et al. (1980)	P	70	1 993	0.25
Adorján, Barna & Hargitay (1978)	R	70	6 365	0.126
Bauer & Östling (1970)	R	70	13 434	0.030
<i>Calculations per unit dextran</i>				
Ring & Messmer (1977)	P	60/75	34 621	0.017
Ring & Messmer (1977)	P	40	51 261	0.002
Ljungström et al. (1983)	R	70	488 748	0.025
Ljungström et al. (1983)	R	40	159 008	0.013

reliable incidence figures for the infrequent severe reactions cannot be derived from studies on small number of patients, e.g. less than 10 000. Clustering of reactions to certain geographical areas and/or periods of time, as well as differently designed studies, may well account for the differences seen between the results of Gruber et al. (1980), Adorján et al. (1978) and Bauer & Östling (1970). The incidence figure for severe DIAR caused by dextran 70 in this study is of the same magnitude as the results for dextran 60/75 in Germany reported by Ring & Messmer (1977).

The indication for dextran 70 was thromboembolic prophylaxis in 56% of patients with DIAR. Thromboembolic prophylaxis with dextran 70 has been recommended to be performed with the infusion of 2–3 units over a period of 1–2 days (Ahlberg et al., 1968; Ljungström, 1977). Thus, it seems valid to assume that the average number of units of dextran 70 per patient was between one and a half and two. This means that the incidence of severe DIAR derived from the present investigation is equivalent to 0.037 to 0.050% per patient treated with dextran 70.

For dextran 40 we found an incidence of severe DIAR of 0.013% per unit supplied. A lower figure, 0.002%, reported by Ring & Messmer (1977) may be due to differences of treatment schedules for e.g. stroke cases in Germany and Sweden. Improvement of microcirculation was the indication for dextran infusion in 62% of the patients with DIAR after dextran 40. Our results suggest that the incidence of severe and fatal DIAR per patient is of the same magnitude for dextran 40 and 70. There is also no theoretical ground for any major difference.

Symptoms

The present investigation confirms that allergic skin manifestations are predominant symptoms in DIAR and that respiratory symptoms also are common (Hedin, 1977; Ring & Messmer, 1977; Furhoff, 1977). DIAR occurring after infusion of minimal amounts of dextran or instantaneously after the start of infusion tend to develop to more severe reactions (Hedin, 1977; Furhoff, 1977). It is noteworthy that in three fatal cases the reaction was initiated by a "biological test dose" of only 0.5–1 ml. Severe reactions occurred after even smaller volumes. Our present concept on the immunologic mechanism of severe DIAR (Richter et al., 1981) strongly indicates that biological test doses should be avoided. In fact, a predisposed patient may be more endangered by a test dose than by a rapid infusion of a larger volume of dextran.

The adverse reactions characterized by fever and/or shivering constitute 5% of the reports. The typical patient is a male who has tolerated the infusion of several units of clinical dextran, but suddenly at the start of a subsequent bottle develops higher fever (40°C), chills and sometimes also slight respiratory distress or erythema. The symptoms disappear gradually after interruption of the infusion, but may return immediately on starting a new infusion of dextran. In the majority of cases the dextran unit causing the symptoms was returned to the manufacturer with request for a pyrogen test. These tests were performed both on rabbits and with a highly sensitive *Limulus* lysate (van Noordwijk & de Jong, 1976). They were negative on every occasion. The pathomechanism of these reactions is at present uncertain.

Identification of the patient at risk

We confirm the finding of Hedin (1977) and Ring (1978) that a history of allergic disease does not predispose to severe DIAR. In patients with grades I+II reactions a history of allergic disease was three times more frequent than in patients with grades IV+V reactions. This is in agreement with Hedin (1977) and Ring (1978) who also reported an overrepresentation of allergic diseases in DIAR of grade I.

An elderly male patient with complicating diseases such as diabetes, chronic inflammation, cardiovascular and/or pulmonary disease is the patient most at risk to develop a severe DIAR. Despite the fact that the clinical characteristics of the patient at risk also fit the patient who is most at risk for postoperative thromboembolic complications, the risk/benefit ratio is greatly in favour of dextran prophylaxis.

Bauer & Östling (1970) emphasized that dextran infusion should be started after the start of anaesthesia and operation in order to minimize the risk for DIAR. We found no evidence that patients under anaesthesia or during operation have a lower incidence of severe DIAR in relation to mild DIAR than non-anaesthetized patients. On the contrary, severe DIAR were significantly more frequent in patients during anaesthesia and operation. Among the patients who developed fatal DIAR under anaesthesia all but one were under epidural or spinal anaesthesia. This is in contrast to the other groups of DIAR, in all of which general anaesthesia was more common than regional. A possible explanation might be that a high spinal or epidural block will reduce adrenal response to shock (cf. Kehlet, 1978). However, these types of anaesthesia are used preferably for patients who are bad risks and this may have influenced our findings.

Pathomechanism

In an early study on DIAR a puzzling finding was that many patients who tolerated dextran had high titres of dextran reactive antibodies (DRA) in their sera (Jacobsson & Zsiga, 1958). It is now evident that severe DIAR only occur in patients with elevated DRA titres, and that these reactions should be classified as immune complex (type III) anaphylaxis (Hedin & Richter, 1982). DRA may represent cross-reacting antibodies induced by infection with bacteria containing polysaccharides with antigenic determinants of dextran. DRA may also be induced

by native dextran occurring in the gastrointestinal tract or ingested as a contaminant of sucrose. When a predisposed patient with a high titre of DRA of IgG class (Hedin et al., 1979; Kraft et al., 1982) is infused with clinical dextran, large noxious immune complexes may be formed with subsequent activation of plasma enzyme systems and thrombocytes leading to clinical symptoms. In mild DIAR (grades I+II) DRA are considered to be of minor or no importance. The term "anaphylactoid" thus seems appropriate only in this category where the pathomechanism still remains unclear.

Therapeutic measures

Revenäs et al. (1980) found very high concentrations of circulating catecholamines during anaphylaxis induced by dog albumin in monkeys. This may indicate that the injection of sympathomimetic drugs during therapy of anaphylaxis only adds a small fraction to an already high concentration of circulating catecholamines. In our study catecholamine therapy has not been shown to have contributed to the favourable outcome in grade IV compared to grade V reactions. Likewise, we found no relation between the administration of corticosteroids and successful resuscitation in severe DIAR. However, in this type of retrospective study the possibility of detecting a valuable therapeutic effect is limited.

The infusion of large volumes of crystalloid solutions to correct hypovolemia seems to have played a role in the survival of some of the patients with severe reactions. However, a difference seen between therapeutic measures used for grades IV and V reactions may also reflect that resuscitations were interrupted earlier due to lack of therapeutic response in patients with grade V reactions.

Metabolic acidosis develops rapidly in patients with severe DIAR. Apparently the degree of acidosis was often underestimated. It is beyond the scope of this study to give a detailed program for the therapy of DIAR of different grades of severity. It appears that in mild reactions interruption of the infusion and symptomatic therapy is adequate. In severe DIAR rapid volume replacement and generous buffer administration seem to be the most important measures apart from artificial ventilation with oxygen, cardiac massage, defibrillation etc.

Since the pathomechanism of severe DIAR has been clarified, a specific prophylaxis based on hapten inhibition has been worked out (Richter,

1973; Ljungström et al., 1983; Renck et al., 1983a and b). For a recent review on dextran hypersensitivity, see Richter & Hedin (1982).

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