COMPLEMENT-MEDIATED REACTIONS TO DIAZEPAM WITH CREMOPHOR AS SOLVENT (STESOLID MR)

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SUMMARY
Changes in complement reactions are described in two patients exhibiting adverse reactions to Stesolid MR (diazepam with Cremophor as solvent). The recorded frequency of adverse reactions to Althesin, propanidid and Stesolid MR suggests that the common solvent Cremophor is responsible for the adverse reactions.

It is known that i.v. injections of Stesolid (diazepam in glycoferol–alcohol–benzoic acid) frequently cause thrombophlebitis (Graham, Pagano and Conner, 1978). Assuming that the solvent system was responsible for this complication, Dumex Ltd (Copenhagen) produced an alternative formula of injectable diazepam. In this preparation (Stesolid MR) the original solvent system was replaced by a macrogol (Cremophor El) which resulted in a considerable decrease in the frequency of thrombophlebitis (Siebke, Ellertsen and Lind, 1976). Since 1976 we have used Stesolid MR as a sedative for endoscopy and our observations have confirmed that the preparation produces a smaller frequency of thrombophlebitis.

Unfortunately, the new preparation appears more liable to cause adverse systemic reactions. Following the administration of 5200 ampoules, we noted five anaphylactoid reactions three of which resulted in circulatory collapse (Schou Olesen and HütteL, 1978). These episodes resembled immediate hypersensitivity reactions. However, one of the patients had not previously received Stesolid MR or any other diazepam preparation.

Watkins and others (1976) have shown that Althesin may activate complement C3 (alternative pathway) and since Althesin and Stesolid MR have the solvent Cremophor in common, we suspected that complement activation could cause the circulatory collapse. Since then we have had the opportunity to study another two patients who also developed adverse reactions to Stesolid MR.

METHODS
Venous blood was collected into tubes containing EDTA as soon as possible after the reaction and three further blood samples were collected over the next 24 h. A final sample was taken not sooner than 5 days after the incident to provide “baseline” values for the patient. Plasma was separated by centrifugation at 1500 g for 10 min and either analysed within 30 min or stored at —60 °C and then thawed immediately before analysis. This took place within 1 week after sampling. C1, C1q, C3 proactivator, C3 and C4 were estimated.

Analyses were performed by rocket immunoelectrophoresis as outlined by Laurell (1966), using monospecific antisera against C1 esterase inactivator, C3, C3 proactivator and C4 (Behringwerke A.G., Marburg, W. Germany). C1q was determined by Mancini radial immunodiffusion techniques (Mancini, Carbonara and Heremans, 1965) using the appropriate monospecific antiserum (Behringwerke). The degree of C3-conversion was estimated by two-dimensional immunoelectrophoresis (Axelsen, Krell and Weeke, 1973) using C3 antiserum (Behringwerke).

RESULTS
The first patient was a 30-yr-old fit male with no history of allergy. Immediately after i.v. injection of Stesolid MR 10 mg he developed a diffuse rash on the face, neck and chest wall, rapidly followed by generalized rash. He complained of respiratory distress and bronchospasm developed. The radial pulse became weak, heart rate increased to 150 beat min⁻¹ and the systolic arterial pressure was 40 mm Hg. He remained conscious and after treatment with oxygen by mask, hydrocortisone, metaxoxide and theophylline i.v., his condition improved and the following day he was discharged in good health.

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C1, C1q and C4 showed minor variations (fig. 1) during the following 24 h and all were within normal range. The C3-activator concentration was found to be small although within normal range, while C3 was below the normal range and remained low compared with the "base-line" value. The two-dimensional immunoelectrophoresis revealed the preponderance of the electrophoretically faster C3o protein in the plasma immediately following the reaction (fig. 2). After 24 h only a small amount of C3o remained.

The second patient was a 32-yr-old previously healthy woman with no history of allergy. She had received Stesolid MR on a previous occasion without incident. Two minutes after an i.v. injection of Stesolid MR 10 mg she developed a generalized erythematous rash and complained of dizziness, abdominal pain and tingling of fingers and toes. A few minutes later facial oedema developed, the pulse became weak and the heart rate increased to 140 beat min⁻¹. Systolic arterial pressure decreased to 70 mm Hg. Breathing was normal and no bronchospasm was noted. Oxygen was given by mask and hydrocortisone 100 mg was administered i.v. She remained conscious and soon recovered apart from facial oedema, which persisted for 2 days.

There was no sign of C3 conversion in this patient. Complement was activated in a classical way, and these changes persisted for more than 24 hr. This may reflect an immune-mediated reaction with secondary complement involvement, since the patient had received Stesolid MR on a previous occasion.

**DISCUSSION**

Watkins, Ward and Appleyard (1977) have found that adverse reactions to Althesin seem to be predominantly mediated by complement C3 activation, although a small proportion of these reactions do appear to be immune-mediated (Watkins et al., 1976).

Reports of adverse reactions to diazepam have been extremely rare (Milner, 1977), but we have shown that Stesolid MR can activate C3 complement. The recorded frequency of adverse reactions to Althesin, propanidid and Stesolid MR (Schou Olesen and Hüttel, 1978) suggests the common solvent Cremophor is responsible for the adverse reactions. If this is verified, more acceptable solvents are required.

**REFERENCES**


ADVERSE REACTIONS TO CREMOPHOR EL


REACTIONS ALEXINES-INTERMEDIAIRES AU DIAZEPAM AYANT LE CREMOPHOR COMME SOLVANT (STESOLID MR)

RESUME

On décrit dans cet article les changements qui ont eu lieu dans les réactions alexines de deux patients réagissant mal au Stesolid MR (diazépam ayant du Crémophor comme solvant). Etant donné la fréquence des réactions adverses enregistrées à l’Althesine, au Propanidid et au Stesolid MR, il semblerait que le Crémophor, solvant commun dans chacun des cas, soit responsable de ces réactions.