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(56) Documents Cited:
WO 2004/047778 A **DE 010204696 A**
FR 002316923 A
WPI Accession No 1994-125274/15 & SU 1635330 (LENGD HAEM. & BLOOD TRANSF. RES.)
Biorheology (2004) Vol 41, pp 53-64, "Blood solule drag-reducing polymers...", Kameneva et al
Journal of Surgical Research (1995), Vol 59, pp 153-158, "PEG-BP-30 monotherapy attenuates the...", Espat et al
Clinical Science (2004), Vol 107, pp 263-272, "Plasma expansion by polyethylene-glycol...", Assaly et al

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Other: **EPODOC, WPI, BIOSIS, MEDLINE, CAPLUS**

(54) Abstract Title: **Medicament for treatment of inflammatory diseases**

(57) An aqueous solution of at least one polyether polyol in a fluid for administration to a human being.

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Figure 1

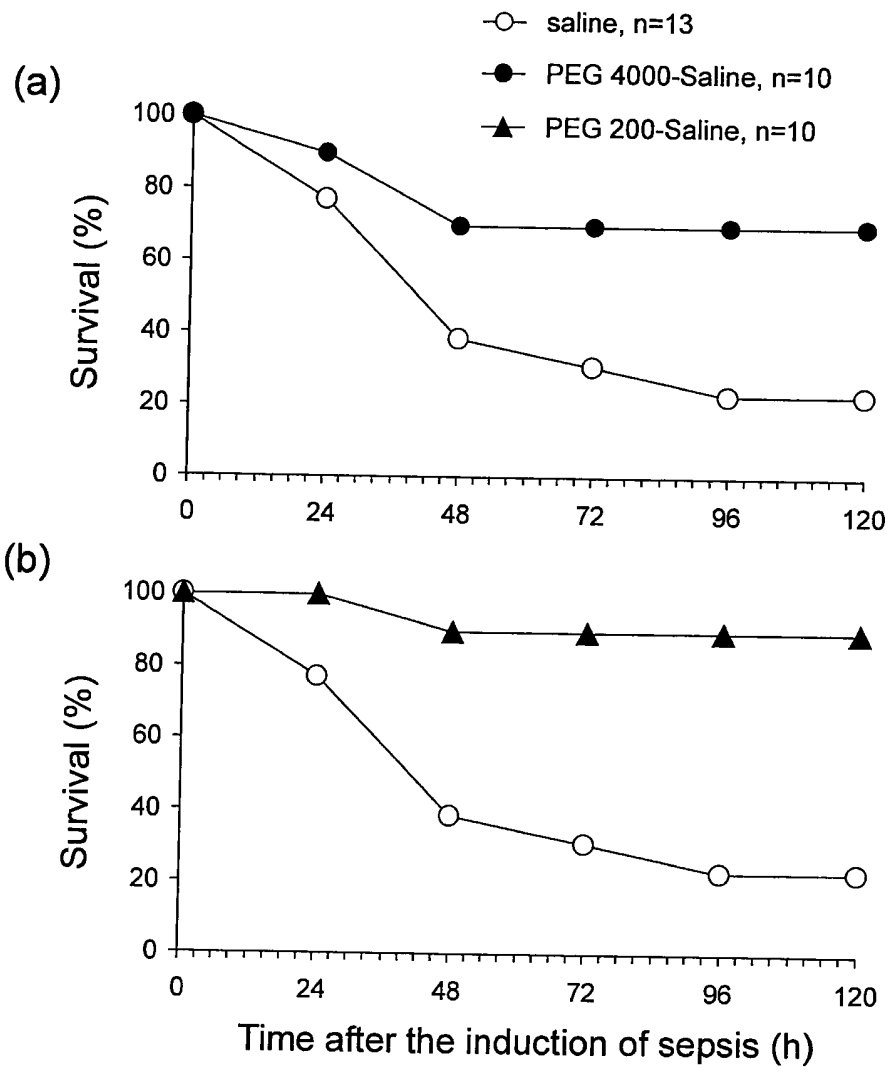

saline, n=13
PEG 4000-Saline, n=10
PEG 200-Saline, n=10
(a)
(b)
Survival (%)
100
80
60
40
20
0
0
24
48
72
96
120
Time after the induction of sepsis (h)

Figure 2

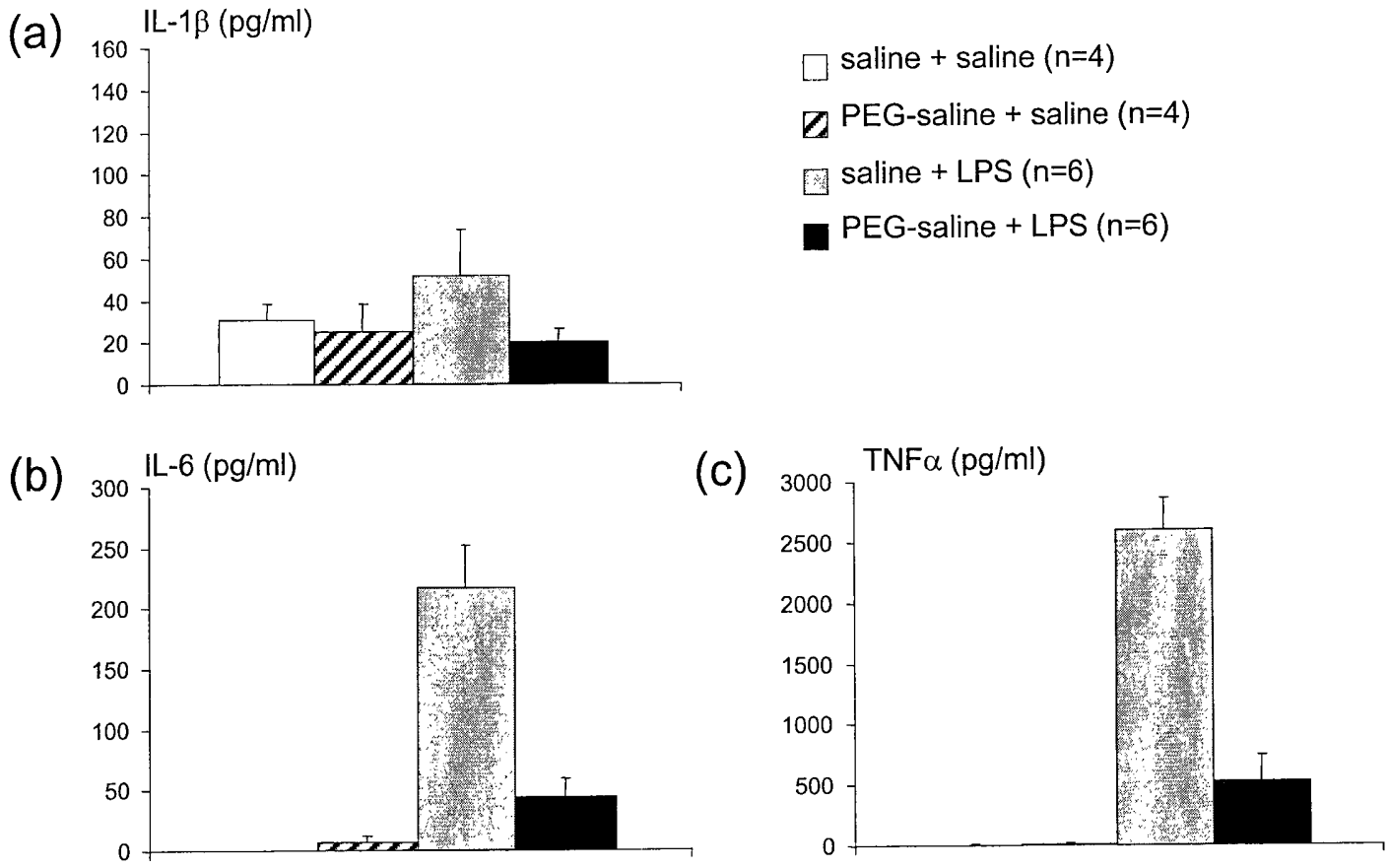

(a)
IL-1β (pg/ml)
160
140
120
100
80
60
40
20
0
saline + saline (n=4)
PEG-saline + saline (n=4)
saline + LPS (n=6)
PEG-saline + LPS (n=6)
(b)
IL-6 (pg/ml)
300
250
200
150
100
50
0
(c)
TNFα (pg/ml)
3000
2500
2000
1500
1000
500
0

Figure 3

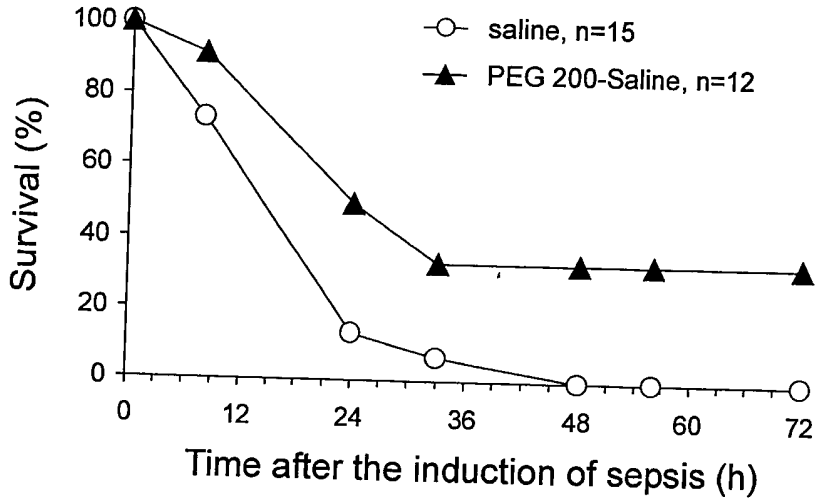
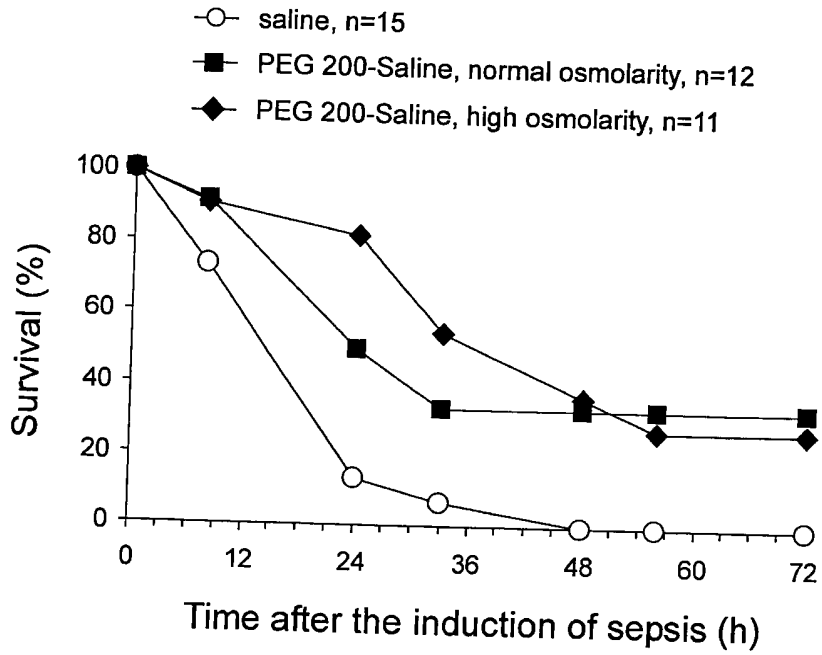


Figure 4



MEDICAMENT FOR TREATMENT OF INFLAMMATORY DISEASES

The present invention relates to a medicament for the treatment of inflammatory diseases and to the use of such a medicament for the treatment of inflammatory diseases.

The hallmark of acute medical and surgical emergencies is the generation of massive quantities of inflammatory mediators, initiated by cytokines. Across a range of both acute and chronic diseases, high levels of inflammation result in premature death or costly morbidity. Currently, 215,000 deaths from sepsis occur in the US alone with associated healthcare costs of $16.7 billion - in total, critically ill patients consume 0.6-1.0% of US GDP per annum. Similarly, in the UK sepsis accounts for up to 11% of all hospital or intensive care admissions. The incidence of sepsis is projected to increase by 1.5% per annum. Despite intensive research efforts over the past 25 years, mortality and morbidity from sepsis, after massive trauma or major surgery, remains high. Sepsis in the intensive care unit typically results in 50% mortality. A key, universally accepted component of treating these common clinical problems is the administration of fluid. Despite being a central part of many medical management strategies, little research has been undertaken to add anti-inflammatory properties to the fluids that are in any event always administered to critically ill patients.

In a paper entitled "Survival in a rat model of lethal hemorrhagic shock is prolonged following resuscitation with a small volume of a solution containing a drag-reducing polymer derived from aloe vera", Carlos A. Macias et al., Shock, Vol. 22, No. 2, pp. 151-156, 2004, the use of resuscitation solutions containing a drag-reducing polymer derived from aloe vera is disclosed for treating rats in a laboratory model of haemorrhage. However, the experimental data showed rather equivocal results with regard to the results using the drag-reducing polymer as compared to saline as a control. Also, the results were a laboratory model of haemorrhage. There is no result directly addressing the treatment of acute or chronic inflammatory conditions.

There is a need for improved treatment of major acute and chronic inflammatory conditions, in particular for surgical and medical emergencies, and for chronic inflammatory disease.

There is also a need for such a treatment that can attenuate and/or resolve major acute and chronic inflammatory conditions.

There is further a need for such a treatment that can be administered readily and effectively.

There is yet further a need for such a treatment that can be administered using as active component a readily available compound, known to be safe for use both in foods and in drugs for administration to humans.

The present invention at least partially aims to meet at least one of those needs.

In a first aspect, the present invention provides an aqueous solution of at least one polyether polyol in a fluid for administration to a human being.

In a second aspect, the present invention provides an aqueous solution of at least one polyether polyol in a fluid for administration to a human being for use as a medicament.

In a third aspect, the present invention provides the use of an aqueous solution of at least one polyether polyol in a fluid for administration to a human being for the manufacture of a medicament for treating inflammatory diseases.

In a fourth aspect, the present invention provides a composition comprising at least one polyether polyol and an aqueous fluid for administration to a human being as a combined preparation for the simultaneous, separate or sequential use as a medicament, in particular for treating inflammatory diseases.

In a fifth aspect, the present invention provides the use of a composition comprising at least one polyether polyol and an aqueous fluid for administration to a human being for the manufacture of a combined preparation for the simultaneous, separate or sequential use as a medicament for treating inflammatory disease.

In accordance with these aspects of the present invention, the polyether polyol may comprise a single polyether polyol, or may comprise a mixture of at least two polyether polyols. The polyether polyol is preferably a polyether glycol, most preferably

polyethylene glycol. The polyethylene glycol preferably has a molecular weight of from 200 to 35000, more preferably from 200 to 4000, and most preferably from 200 to 1000.

The present invention may employ a "low molecular weight polyethylene glycol", meaning the range of molecular weight of the polyethylene glycols is from 200 to 1000, or alternatively the present invention may employ a "high molecular weight polyethylene glycol", meaning the range of molecular weights of the polyethylene glycol is from 1000 to 35000. A mixture of such a "low molecular weight polyethylene glycol" and a "high molecular weight polyethylene glycol" may alternatively be employed.

The aqueous fluid for administration to a human being is a medical-grade liquid, such as an aqueous intravenous resuscitation fluid or an aqueous fluid for intrathecal or intraperitoneal therapy which preferably comprises an aqueous solution of one or more crystalloids, an aqueous colloid suspension of one or more colloids, or a mixture of such an aqueous solution of one or more crystalloids and such a colloid suspension of one or more colloids. Preferred aqueous crystalloid solutions include Ringer's lactate solution, compound sodium lactate solution (for example comprising sodium 131 mmol/l, potassium 5 mmol/l, calcium 2 mmol/l, chloride 111 mmol/l, lactate 29 mmol/l; pH 6-7; osmolarity 278 mOsmol/l) and normal saline solution (for example 0.9% sodium chloride in water), or mixtures of two or more of these solutions. Preferred aqueous colloid suspensions include succinylated gelatine suspended in, for example 0.9% saline solution and starch based colloid preparations (including hydroxyethylated starch) in aqueous suspension. The preferred crystalloid-colloid solutions include one or more aqueous crystalloid solutions in admixture with one or more aqueous colloid suspensions.

Preferably, at least one polyether polyol is dissolved in the aqueous fluid for administration to a human being in a concentration (with respect to the volume of the initial aqueous fluid) of from 1 to 1000 mg/ml, more preferably from 1 to 50 mg/ml, yet more preferably from 1 to 10 mg/ml.

When the present invention employs a "low molecular weight polyethylene glycol", as hereinbefore defined, preferably the polyether polyol is dissolved in the aqueous fluid for administration to a human being in a concentration from 1 to 1000 mg/ml, more preferably from 1 to 50 mg/ml, yet more preferably from 1 to 10 mg/ml.

When the present invention employs a "high molecular weight polyethylene glycol", as hereinbefore defined, preferably the polyether polyol is dissolved in the aqueous fluid for administration to a human being in a concentration from 1 to 1000 mg/ml, more preferably from 1 to 50 mg/ml, yet more preferably from 1 to 10 mg/ml.

In a sixth aspect, the present invention provides a method of treating inflammatory disease, or diseases having inflammatory effects, the method comprising administering the medicament solution of the present invention to a patient.

For treating inflammatory disease, or conditions having inflammatory components, the medicament solution of the present invention is preferably administered intravenously, intraperitoneally or intrathecally for central nervous system administration. The administration method is the same as for the conventional administration of an intravenous resuscitation fluid or administration of intrathecal or intraperitoneal therapy. The administration may be in a single dose, or in plural doses administered over a period of time.

Embodiments of the present invention will now be described by way of example only with reference to the accompanying drawings, in which:

Figures 1 (a) and (b) show the relationship between survival rate and time for mice treated with a medicament in accordance with Example 1 of the present invention and in a comparative control sample;

Figures 2 (a), (b) and (c) show the relationship between respective cytokines and composition of the injection for rats treated with a medicament in accordance with Example 2 of the present invention and in comparative control samples;

Figure 3 shows the relationship between survival rate and time for mice treated with a medicament in accordance with Example 3 of the present invention and in a comparative control sample; and

Figure 4 shows the relationship between survival rate and time for mice treated with a medicament in accordance with Example 4 of the present invention and in a comparative control sample.

The present invention is predicated on the finding by the present inventors that there is a marked benefit resulting from the administration of polyether polyol, in particular polyethylene glycol (PEG)-saline solutions in experimental models of acute inflammation, including prevention of death in lethal inflammation/sepsis. The therapeutic application of this finding uses widely practiced, accepted means of maintaining/restoring organ function through administration of fluid, for example as a resuscitation fluid, but with the additional benefit of anti-inflammatory substance within that fluid.

The present invention therefore is based in part on the discovery of a new and unexpected medical use of a known compound, which, according to the experimental data obtained by the present inventors, has profound anti-inflammatory properties, which to the inventors' knowledge was previously unrecognised by those skilled in the art. In accordance with the present invention, the polyethylene glycol-saline solution can be administered easily, safely and effectively. The inventors believe that because polyethylene glycol has previously been recognised as being safe for human use, being used widely in foods and drugs (categorised as a "GRAS" (Generally Recognised as Safe) substance by The United States Food and Drug Administration), there is an immediate clinical opportunity to develop polyethylene glycol-saline solutions as a life-saving therapeutic intervention in critically ill individuals. Moreover, the administration of the polyether polyol-saline solutions may readily be achieved using a standard mode of care (fluid therapy) to deliver, in a resuscitation fluid, the additional anti-inflammatory benefit of the polyether polyol compounds.

Polyether polyol, in particular polyether glycol, and most particularly polyethylene glycol, is a widely used substance for both household and industrial purposes. It possesses some remarkable properties that have been explored in several laboratory-based scenarios, although the mechanisms through which polyethylene glycol acts under different experimental conditions are unclear. Polyethylene glycol improves function in experimental transplant organs (JP Faure et al, American Journal of Transplantation 2004 vol 4; 495-504) reverses experimental spinal cord injury (R Borgens and R Shi, FASEB J. vol 14, 27–35, 2000) and protects against experimentally-induced colonic cancer (DE

Corpet et al, Carcinogenesis vol.20 no.5 pp.915–918, 1999). Regardless of the underlying mechanism, the data obtained experimentally by the present inventors shows that tiny amounts of polyethylene glycol, dissolved in fluid used internally for resuscitation (for example an aqueous solution of one or more crystalloids, can aqueous suspension of one or more colloids, or a mixture thereof), prevents death in experimental models of severe sepsis even when it is administered 2 hours after the induction of sepsis.

The medicament of the present invention may be used for its anti-inflammatory properties for the treatment of pathophysiological states where there is acute and/or chronic release of inflammatory mediators, including diseases or conditions such as, for example: sepsis/septic shock; acute respiratory distress syndrome; major surgical procedures associated with major inflammatory response e.g. cardiac surgery requiring cardiopulmonary bypass, major polytrauma, etc.; prevention of peritoneal adhesions; acute myocardial infarction; pancreatitis; burns; stroke/acute brain injury; and chronic pain.

The present invention will now be described in greater detail with reference to the following non-limiting Examples.

Example 1

Two isotonic solutions of polyethylene glycol in Ringer's lactate solution in accordance with the present invention were prepared. A first solution had a concentration of 6.2 mg/ml of the polyethylene glycol in Ringer's lactate solution, and the polyethylene glycol had an average molecular weight of 200, and is available in commerce from the company Sigma, of Poole, UK (amongst many others). This polyethylene glycol solution is referred to hereinafter in these Examples as PEG 200-saline. A second solution had a concentration of 6.2 mg/ml of the polyethylene glycol in the Ringer's lactate solution, and the polyethylene glycol had an average molecular weight of 4000, and is available in commerce from the company Sigma, of Poole, UK (amongst many others). This polyethylene glycol is referred to hereinafter in these Examples as PEG 4000-saline.

Adult mice were injected intraperitoneally with zymosan, which induces severe inflammation leading to systemic bacteraemia and endotoxaemia from gastrointestinal inflammation, with a predicted mortality of 80% by day 5.

The isotonic PEG-saline solution was administered intraperitoneally (25 ml/kg) 2 hours after the onset of peritonitis (and twice daily thereafter, every 12 hours). This administration protocol represented both a realistic clinical and therapeutic timeframe of events. Ten mice (i.e. n = 10) were administered the low molecular weight (200) polyethylene glycol-saline solution (the first solution) and another ten mice (i.e. n = 10) were administered the high molecular weight (4000) polyethylene glycol-saline solution (the second solution). A further thirteen mice (i.e. n = 13) were administered, as a control, the saline solution alone, not containing any polyethylene glycol.

The results are summarised in Figures 1 (a) and (b), which show survival plots depicting percentage of mice alive vs. time after the onset of sepsis. Numbers in parentheses indicate sample sizes at the outset of the experiment. It was found that this administration of the isotonic polyethylene glycol-saline solution reduced mortality by 55-75% (depending on the molecular weight of polyethylene glycol). The low molecular weight (200) polyethylene glycol tended to result in a higher survival rate than the high molecular weight (4000) polyethylene glycol.

This Example shows that administration of a polyethylene glycol-saline solution in accordance with the present invention can substantially reduce mortality in a clinically relevant model of severe inflammation and sepsis.

Example 2

In this Example it was found that bacterial endotoxin lipopolysaccharide (LPS)-evoked production and/or release of key pro-inflammatory mediator cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumour necrosis factor-α (TNFα) are markedly reduced by polyethylene glycol 200 -saline solution (using the low molecular weight polyethylene glycol used in the first solution of Example 1) treatment in rats.

In this Example, rats were injected sequentially with either (a) saline and saline (n = 4); (b) the low molecular weight (200) polyethylene glycol-saline solution (10% PEG in a dose of 1 ml/kg) and saline (n = 4); (c) saline and bacterial endotoxin – *E.coli* lipopolysaccharide (LPS, 50 μg/kg) – dissolved in saline (n = 6); or (d) the low molecular weight (200)

polyethylene glycol-saline solution and bacterial endotoxin – *E.coli* lipopolysaccharide (LPS, 50 μg/kg) – dissolved in saline (n = 6). Plasma IL-1β, IL-6 and TNFα concentrations were measured after a period of 1 hour following injection of the respective solutions (containing LPS or not). The results are summarised in Figures 2 (a), (b) and (c), which show data presented as means $\pm$ standard errors of the means. Numbers in parentheses indicate sample sizes.

It was found that IL-1β, IL-6 and TNFα levels in plasma of rats treated with both polyethylene glycol 200-saline solution and lipopolysaccharide were significantly lower than in plasma of rats injected with saline and lipopolysaccharide ($p<0.05$).

This Example shows that administration of a polyethylene glycol-saline solution in accordance with the present invention can substantially reduce the production and/or release of pro-inflammatory cytokines during systemic inflammation evoked by bacterial endotoxins.

Example 3

Experimental endotoxaemic sepsis has been shown to cause higher mortality in female animals (MK Angele et al., Vol 14 Shock pp. 81–90, 2000). Female mice were injected intraperitoneally with lethal dose (2.5 mg/kg) of *E.coli* endotoxin lipopolysaccharide, followed 2 hours later with fluid resuscitation of either saline (n = 15) or the low molecular weight (200) polyethylene glycol-saline solution (the first solution of Example 1) (n = 12). The mice were injected intraperitoneally twice daily thereafter.

The results are summarised in Figure 3.

All control (i.e. saline treated) mice died within 48 h after lipopolysaccharide injection, while ~35% of polyethylene glycol 200-saline administered animals survived and completely recovered.

It should be noted that endotoxin given intraperitoneally is cleared by residual macrophages within minutes and would not be present in the peritoneal cavity at the time when the first injection of polyethylene glycol-saline is done. Thus, without being bound by theory, the

inventors believe that direct neutralization of lipopolysaccharide or blockade of its interaction with the receptor by polyethylene glycol is unlikely, and that it is more feasible that polyethylene glycol-saline exerts its protective effect by counteracting inflammatory process triggered by lipopolysaccharide following absorption.

This Example shows that administration of a polyethylene glycol-saline solution in accordance with the present invention can substantially reduce mortality in lethal endotoxaemia in sepsis-hypersensitive animals.

Example 4

Hyperosmolar fluid resuscitation has been reported previously to reduce experimental inflammation in comparison to resuscitation with solutions of normal osmolarity. However, no difference in survival was found when sepsis-hypersensitive female mice exposed to lethal endotoxaemia (2.5 mg/kg *E.coli* lipopolysaccharide) were resuscitated with either isomolar [similar osmolarity as normal blood; 293 mOsmol/l, 6.2 mg/ml PEG 200 or hyperosmolar (higher osmolarity than normal blood; 318 mOsmol/l, 5% PEG 200 w/v) polyethylene glycol-saline solution (using twice daily intraperitoneal injections). The polyethylene glycol was the same low molecular weight (200) polyethylene glycol as used in the first solution of Example 1.

The results are summarised in Figure 4. In both isomolar and hyperosmolar polyethylene glycol-saline treated groups (n=11-12 mice), mortality was reduced by the same extent. Approximately 30% of sepsis-hypersensitive female mice treated with polyethylene glycol-saline solutions fully recovered from lethal endotoxaemia. In the control saline-treated group (n = 15) no animals survived beyond the 48 hour time point. These results suggest that PEG is the key component, rather than osmolarity effects, in protecting against inflammation.

These Examples show that treatment with polyethylene glycol-saline solutions markedly reduced mortality in two different experimental models of severe acute systemic inflammation and sepsis. The polyethylene glycol-saline was found to protect against lethal endotoxaemia in 30% of mice and almost abolished mortality in zymosan-induced experimental peritonitis, where 80% mortality is expected. Endotoxin-induced production

of pro-inflammatory cytokines was inhibited, through systemic actions of polyethylene glycol-saline. From these data the inventors conclude, without being bound by theory, that the protective effect of polyethylene glycol-saline infusion in severe inflammatory conditions is due to inhibition of overzealous production and/or release of harmful quantities of pro-inflammatory cytokines.

It is believed that the present Examples demonstrate that a polyethylene glycol-saline fluid decreases production of pro-inflammatory mediators and prevents death in severe sepsis. The implications of the data are far reaching, with immediate commercial and clinical applications, as would be apparent to medical practitioners.

CLAIMS:

1. An aqueous solution of at least one polyether polyol in a fluid for administration to a human being.

2. An aqueous solution of at least one polyether polyol in a fluid for administration to a human being for use as a medicament.

3. An aqueous solution according to claim 1 or claim 2 wherein the polyether polyol comprises a single polyether polyol, or a mixture of at least two polyether polyols.

4. An aqueous solution according to any one of claims 1 to 3 wherein the polyether polyol is a polyether glycol.

5. An aqueous solution according to claim 4 wherein the polyether polyol is polyethylene glycol.

6. An aqueous solution according to claim 5 wherein the polyethylene glycol has a molecular weight of from 200 to 35000.

7. An aqueous solution according to claim 6 wherein the polyethylene glycol has a molecular weight of from 200 to 4000.

8. An aqueous solution according to claim 7 wherein the polyethylene glycol has a molecular weight of from 200 to 1000.

9. An aqueous solution according to any foregoing claim wherein the aqueous fluid for administration to a human being is an aqueous intravenous resuscitation fluid or an aqueous fluid for intrathecal or intraperitoneal therapy.

10. An aqueous solution according to claim 9 wherein the aqueous fluid for administration to a human being is an aqueous solution of one or more crystalloids, an aqueous colloid suspension of one or more colloids, or a mixture of such an aqueous solution of one or more crystalloids and such a colloid suspension of one or more colloids.

11. An aqueous solution according to any foregoing claim wherein the at least one polyether polyol is dissolved in the aqueous fluid for administration to a human being in a concentration (with respect to the volume of the initial aqueous fluid) of from 1 to 1000 mg/ml.

12. An aqueous solution according to claim 11 wherein the at least one polyether polyol is dissolved in the aqueous fluid for administration to a human being in a concentration (with respect to the volume of the initial aqueous fluid) of from 1 to 50 mg/ml.

13. An aqueous solution according to claim 12 wherein the at least one polyether polyol is dissolved in the aqueous fluid for administration to a human being in a concentration (with respect to the volume of the initial aqueous fluid) of from 1 to 10 mg/ml.

14. Use of an aqueous solution of at least one polyether polyol in a fluid for administration to a human being for the manufacture of a medicament for treating inflammatory diseases.

15. Use of a composition comprising at least one polyether polyol and an aqueous fluid for administration to a human being for the manufacture of a combined preparation for the simultaneous, separate or sequential use as a medicament for treating inflammatory disease.

16. Use according to claim 14 or claim 15 wherein the polyether polyol comprises a single polyether polyol, or a mixture of at least two polyether polyols.

17. Use according to any one of claims 14 to 16 wherein the polyether polyol is a polyether glycol.

18. Use according to claim 17 wherein the polyether polyol is polyethylene glycol.

19. Use according to claim 18 wherein the polyethylene glycol has a molecular weight of from 200 to 35000.

20. Use according to claim 19 wherein the polyethylene glycol has a molecular weight of from 200 to 4000.

21. Use according to claim 20 wherein the polyethylene glycol has a molecular weight of from 200 to 1000.

22. Use according to any one of claims 14 to 21 wherein the aqueous fluid for administration to a human being is an aqueous intravenous resuscitation fluid or an aqueous fluid for intrathecal or intraperitoneal therapy.

23. Use according to claim 22 wherein the aqueous fluid for administration to a human being is an aqueous solution of one or more crystalloids, an aqueous colloid suspension of one or more colloids, or a mixture of such an aqueous solution of one or more crystalloids and such a colloid suspension of one or more colloids.

24. Use according to any one of claims 14 to 23 wherein the at least one polyether polyol is dissolved in the aqueous fluid for administration to a human being in a concentration (with respect to the volume of the initial aqueous fluid) of from 1 to 1000 mg/ml.

25. Use according to claim 24 wherein the at least one polyether polyol is dissolved in the aqueous fluid for administration to a human being in a concentration (with respect to the volume of the initial aqueous fluid) of from 1 to 50 mg/ml.

26. Use according to claim 25 wherein the at least one polyether polyol is dissolved in the aqueous fluid for administration to a human being in a concentration (with respect to the volume of the initial aqueous fluid) of from 1 to 10 mg/ml.

27. A composition comprising at least one polyether polyol and an aqueous fluid for administration to a human being as a combined preparation for the simultaneous, separate or sequential use as a medicament, in particular for treating inflammatory diseases.

28. A composition according to claim 27 wherein the polyether polyol comprises a single polyether polyol, or a mixture of at least two polyether polyols.

29. A composition according to claim 27 or claim 28 wherein the polyether polyol is a polyether glycol.

30. A composition according to claim 29 wherein the polyether polyol is polyethylene glycol.

31. A composition according to claim 30 wherein the polyethylene glycol has a molecular weight of from 200 to 35000.

32. A composition according to claim 31 wherein the polyethylene glycol has a molecular weight of from 200 to 4000.

33. A composition according to claim 32 wherein the polyethylene glycol has a molecular weight of from 200 to 1000.

34. A composition according to any one of claims 27 to 33 wherein the aqueous fluid for administration to a human being is an aqueous intravenous resuscitation fluid or an aqueous fluid for intrathecal or intraperitoneal therapy.

35. A composition according to claim 34 wherein the aqueous fluid for administration to a human being is an aqueous solution of one or more crystalloids, an aqueous colloid suspension of one or more colloids, or a mixture of such an aqueous solution of one or more crystalloids and such a colloid suspension of one or more colloids.

36. A composition according to any one of claims 27 to 35 wherein the at least one polyether polyol is dissolved in the aqueous fluid for administration to a human being in a concentration (with respect to the volume of the initial aqueous fluid) of from 1 to 1000 mg/ml.

37. A composition according to claim 36 wherein the at least one polyether polyol is dissolved in the aqueous fluid for administration to a human being in a concentration (with respect to the volume of the initial aqueous fluid) of from 1 to 50 mg/ml.

38. A composition according to claim 37 wherein the at least one polyether polyol is dissolved in the aqueous fluid for administration to a human being in a concentration (with respect to the volume of the initial aqueous fluid) of from 1 to 10 mg/ml.

39. A method of treating inflammatory disease, or diseases having inflammatory effects, the method comprising administering the aqueous solution of any one of claims 1 to 13 to a patient.

40. A method according to claim 39 wherein the aqueous solution is administered intravenously, intrathecally or intraperitoneally.

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INVESTOR IN PEOPLE

Application No:	GB0428218.2	**Examiner:**	Richard Sewards
Claims searched:	1-40	**Date of search:**	6 April 2005

Patents Act 1977: Search Report under Section 17

Documents considered to be relevant:

Category	Relevant to claims	Identity of document and passage or figure of particular relevance
X	1-6, 9-13, 27-31 & 34-38	WPI Accession No 1994-125274/15 & SU 1635330 (LENGD HAEM. & BLOOD TRANSF. RES.) See WPI abstract
X	1-6, 9-13, 27-31 & 34-38	Biorheology (2004) Vol 41, pp 53-64, "Blood solule drag-reducing polymers...", Kameneva et al See abstract & discussion
X	1-6, 9-19, 22-31 & 34-40	Journal of Surgical Research (1995), Vol 59, pp 153-158, "PEG-BP-30 monotherapy attenuates the...", Espat et al See whole document
X	1-7, 9-20, 22-32 & 34-40	Clinical Science (2004), Vol 107, pp 263-272, "Plasma expansion by polyethylene-glycol...", Assaly et al See whole document
X	1-6, 11-19, 24-31 & 36-39	FR 2316923 A (SOLOMIDES) see whole document
X	1-8, 11-21, 24-33 & 36-39	DE 10204696 A (SONOMED) see abstract, paras 6-10
X	1-6, 11-19, 24-31 & 36-39	WO 2004/047778 A (UC TECH) see p 3 l 10 - p 4 l 17, p 7 ll 24-31, Example 1

Categories:

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application

Field of Search:

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC^{X} :

A5B

Worldwide search of patent documents classified in the following areas of the IPC^{07}

A61K