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(54) TREATMENT OF IRON DEFICIENCY IN PIGLETS

(71) We, FISONS LIMITED, a British Company, of Harvest House, Felixstowe, Suffolk, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to the prophylactic treatment of iron deficiency in piglets and to compositions for use in such treatment.

A number of preparations containing iron are known and are administered to new born piglets by way of injection. However this method of administration has the drawbacks that it requires a skilled administrator, and sterile conditions, if infection of the piglet is to be avoided. Furthermore injection of certain iron containing preparations may have adverse effects on the piglet, for example they may cause bruising, or staining of the skin or flesh which in turn will detract from the value of the piglet. A further disadvantage is that public health authorities, because of the abuse of drugs by humans, are tending to restrict the supplies of injection syringes to the public. It has not previously been considered practical to administer a single dose of an iron complex (e.g. an iron dextran) to animals orally as in general these compounds are not well absorbed when administered by this route and the treatment is therefore ineffective.

According to the present invention there is provided a method for the prophylactic treatment of iron deficiency in piglets which comprises administering orally to the piglet within 24 hours of its birth a complex containing iron and a polysaccharide, a di-saccharide; a protein or a polypeptide. It is desirable to rear the piglet for at least two weeks after the treatment.

Preferred iron complexes are those in which the iron is associated with a polysaccharide. Complexes which may be mentioned are those containing iron in combination with a dextran, dextrin, polyglucose, polymannose, polymaltose, polysucrose, polygalactose, mannan, galactan, levan, inulin, polyfructose, xylan, araban, an alginate, chrondroitin or pectin. The end groups of the above polysaccharides may, if desired, have been modified, e.g. by hydrogenation, oxidation, alkali degradation, heptonate formation or glycerol glycoside formation; furthermore the polysaccharides may have been modified by substitution reaction for example to give ethers, e.g. carboxyalkyl ethers. Thus more specifically there may be mentioned complexes containing iron and a dextran, e.g. unmodified dextran, alkali degraded dextran, hydrogenated dextran and dextran ethers; or a dextrin, e.g. unmodified dextrin, hydrogenated dextrin, oxidised dextrin and dextrin glycerol glycoside. These complexes may have associated with them one or more other non-toxic polyhydroxy compound, e.g. sucrose, glycol, sorbose, sorbitol, xylose, glucose or galactose; or one or more non-toxic organic acids, e.g. citric, tartaric or aspartic acid. Other iron complexes which may be mentioned include those involving disaccharides or their derivatives, e.g. iron sucroses; and complexes containing iron and a protein or polypeptide, e.g. gelatin. The iron complex should of course have a molecular size in a range which is readily absorbed by the piglet, and the optimum molecular size may be found for each complex by using known techniques. Specific complexes which may be mentioned include those known as "Anfergen V" (an iron dextrin) "Haemigron" (an iron polymaltose) "Pigdex" (a ferric oxide dextrin) "Imposil" (an iron dextran) (Imposil is a Registered Trade Mark) "Rubrafer" and "Ironex" (iron hydrogenated dextrans) "Ferridex" (iron dextran glycerol glycoside) "Idofer" iron polygalactose) and "Astrofer".

The iron complexes to be administered by the method of the invention may if desired be admixed with other compounds which are orally tolerated by the piglet, for example inert diluents, such as talc, dextran, lactose, calcium phosphate, or water. The iron complex may also be admixed with the animals foodstuff, e.g. milk, or with other matter

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which it is desired to administer to the animal orally. Thus the iron complex compound may be admixed with physiologically desirable trace elements such as copper, cobalt, manganese or a mixture thereof; with vitamins, e.g. vitamins A, D, B_1, B_2, B_6, B_{12}, E (or other antioxidants) or a mixture thereof; antibiotics (to prevent a neonatal scour), for example broad spectrum antibiotics such as chlortetracycline hydrochloride, oxytetracycline and nitrofurans; absorption aids, e.g. certain amino acids; and immunoglobulins.

Particular compositions which may be mentioned are fluid compositions, e.g. a drench, which may be administered with a drenching gun or bottle or a similar device adapted to administer a metered dose to the piglet. The drench may be supplied in the form of a wettable powder which can then be dispersed or dissolved in water by the user. Such a powder may comprise the iron complex, a colloid to make the drench of suitable viscosity for the gun, and a surface active agent to assist dispersion or dissolution of the powder in water. The drench may also be supplied in liquid form in which case it is desirable to incorporate a preservative, e.g. chloroform, glycerin or sodium benzoate. The iron complex may also be presented in the following forms:—

as a tablet containing iron complex, binder, moistening agent, disintegrant and lubricant; or

as a capsule containing iron complex, binder, moistening agent and lubricant; or

as a pill or bolus containing iron complex and syrup or treacle; or

as a paste containing iron complex, gum and preservative; or

as an aerosol containing iron complex, surface agent, propellant and optionally water.

The aerosol, drench and paste compositions may also, if desired contain a suitable flavouring to help prevent rejection of the composition by the piglet. The compositions should of course be in such a form that the required dose may be administered easily, e.g. as a single unit dose, to the piglet. Thus, for example unit doses of liquids should be of less than 3 and preferably 0.5 to 2.0 ml. Preferred compositions from the point of view of ease and certainty of administration are those which are solids or pastes.

Thus according to a further feature of the invention we provide a composition which is orally acceptable to the new born piglet which comprises an iron-dextran and a diluent, surface active agent, or carrier, or other matter which is orally acceptable to the piglet, the composition being a solid or paste.

The iron complex may be given to the piglet from 3 to 24 hours, preferably from 3 to 16 hours, e.g. about 8 hours after birth. The dosage of iron compound to be given to the piglet will of course vary with the particular iron compound to be administered, however in general dosages of from 50 to 1,000, preferably from 50 to 300, and most preferably from 100 and 250 mg of iron are satisfactory (the dosage of iron being measured as elemental iron). This dosage may be administered in divided doses, but for convenience will generally be administered in a single dose. We therefore also provide compositions comprising in unit dosage form from 50 to 1,000, preferably from 50 to 300, and most preferably from 100 to 250 mg of iron.

The iron complexes may be administered to the piglet in conventional manner, for example tablets, capsules, pills and boluses may be placed at, or shot or flicked into the back of the animals mouth and pastes may be smeared carefully on tongue, teeth and the inside of the animals mouth. The complexes may also be administered by other techniques, for example liquids and pastes may be administered from a bottle or gun adapted to eject a meter dose, and aerosol compositions may also be put in containers adapted to eject a metered dose. Such bottles, guns and containers containing a composition comprising a suitable iron complex form a further feature of our invention.

The invention is illustrated but in no way limited by the following Examples 1 to 9 in which the "split litter" method was used, unless otherwise specified, and the iron was administered, unless otherwise specified, as "Imposil" (Imposil is a registered Trade Mark) an iron dextran complex (mean molecular weight of the dextran is 3000) containing 10% by weight of iron, or "Imferon" ("Imferon is a registered Trade Mark) an iron dextran complex (mean molecular weight of the dextran is 3000) containing 7.5% by weight of iron, weights are in kg., concentration of haemoglobin (Hb) in g per 100 ml of blood, unless otherwise stated, red blood corpuscles (Rbl) in millions per mm^3 and haematocrit (Haem) as a percentage, i.m. designates intramuscular injection, p.o. oral administration and the dosages are given in terms of iron content.

Example 1

Body weight gain and blood haemoglobin in piglets treated p.o. or i.m. at 3 to 20 hours after delivery are shown in Table I. Five herds and 18 litters were used.

TABLE I

Dose of Fe	150 mg/p.o.	150 mg/i.m.
Body wt. gain		
0 to 3 weeks	4.30 ± 1.24	4.00 ± 1.45
No. of pigs	84	85
Hb at 3 weeks	10.44 ± 1.52	11.35 ± 1.20
No. of pigs	82	84
Body wt. gain		
0 to 8 weeks	12.42 ± 2.85	12.61 ± 2.73
No. of pigs	77	77

Example 2

The procedure of Example 1 was repeated using five herds, 14 litters and different dosages of iron with the results shown in Table II.

TABLE II

Dose of Fe	200 mg/p.o.	150 mg/i.m.
Body wt. gain 0—3 weeks	3.83 ± 1.21	3.54 ± 1.19
No. of pigs	64	66
Hb at 3 weeks	11.21 ± 1.64	11.46 ± 1.29
No. of pigs	63	65
Body wt. gain 0—8 weeks	11.78 ± 4.53	12.04 ± 3.57
No. of pigs	60	64

Example 3

The procedure of Example 1 was repeated save that all piglets (no split litters) were treated at 3 to 10 hours after birth. The same 5 herds (25 litters) were used as in Examples 1 and 2. For comparison the body weights and Hb values of the i.m. treated pigs of Examples 1 and 2 are also given in Table III.

TABLE III

		Examples 1 and 2
Dose of Fe	200 mg/p.o.	150 mg/i.m.
Body wt. at 3 weeks	5.98 ± 1.41	5.17 ± 1.45
No. of pigs	222	151
Hb at 3 weeks	10.77 ± 1.54	11.40 ± 1.18
No. of pigs	213	149

Example 4

Piglets were treated about 8 hours after birth at the dosages and with the results shown in Table IV.

TABLE IV

	Number of pigs	Weight		Hb		Rbl		Haem	
		at birth	3 wks	at birth	3 wks	at birth	3 wks	at birth	3 wks
150 mg i.m.	2	1.03	4.91	10.8	10.1	4.4	3.8	34.0	31.5
150 mg per os	3	1.29	5.60	10.3	9.8	4.2	4.1	34.7	31.0
300 mg per os	5	1.33	4.38	9.8	10.8	4.0	4.1	31.8	33.8

It is clear from the table that all haematological values are satisfactory.

Example 5

Iron dextran was administered orally to piglets 8, 16 and 24 hours after birth. The dose was 150 mg iron. The following results were obtained:

TABLE V

	Number of pigs	Weight		Hb		Rbl		Haem	
		at birth	3 wks	at birth	3 wks	at birth	3 wks	at birth	3 wks
8 hours	6	1.38	6.31	10.5	10.1	4.3	3.9	33.0	31.7
16 hours	7	1.42	5.73	10.4	8.5	4.3	3.3	31.0	28.0
24 hours	6	1.20	4.96	10.3	6.7	4.1	2.6	34.0	20.3

Weight gain and haematological values are best when treatment is given 8 hours after birth.

Example 6

Iron dextran was given to piglets 24 hours after birth. As a positive check use was made of piglets treated i.m. while untreated piglets served as a negative check. The dose was 150 mg iron. The results obtained are given in the Table VI below.

TABLE VI

	Number of pigs	Weight		Hb		Pbl		Haem	
		at birth	3 wks	at birth	3 wks	at birth	3 wks	at birth	3 wks
Per os	7	1.54	5.77	11.4	8.6	5.1	4.6	38.7	29.8
I.m.	6	1.28	5.93	10.5	9.9	4.9	4.6	37.0	34.1
Untreated	11	1.49	4.69	9.99	4.07	4.5	2.35	33.5	15.4

From these data it is evident that positive effects on weight gain and haematological values were achieved in the treated groups. The untreated group developed serious anaemia. Iron was obviously resorbed on administration of iron dextran 24 hours after birth.

For the sake of comparison a further test was made, similar to the above, but with administration 3 days after birth. The results were as follows:

TABLE VII

	Number of pigs	Weight		Hb		Rbl		Haem	
		3 days	3 weeks	3 days	3 weeks	3 days	3 weeks	3 days	3 weeks
Per os	4	1.40	4.99	9.2	6.4	3.52	3.48	28.0	24.0
Untreated	3	1.41	4.76	9.53	5.06	3.86	3.2	27.0	20.0

It is clear from this table that the untreated group is anaemic or, in other words, its blood values are too low. The group treated perorally does not have satisfactory blood values. Administration was judged to have been given too late after birth.

Example 7

The object of this test was to compare firstly the effects of different doses of iron dextran administered orally and secondly the effects of different doses of a preparation, containing ferrous fumarate and intended for oral application, which was given suspended in water about 8 hours after birth. The iron dextran doses used were 150, 450 and 900 mg reckoned as Fe. The dosages of the preparation intended for peroral administrtaion were equivalent to 150, 450 and 900 mg Fe. An untreated group served for comparison. Treatment was given in all cases 8 hours after birth. On account of the large volumes entailed when administering 900 mg Fe as ferrous fumarate, the dose was given in two applications, the amount that the piglets were unable to accept on the first occasion being given to them 6 hours later. The following results were obtained:

TABLE VIII

	Number of pigs	Weight		Hb		Rbl		Haem	
		at birth	3 wks	at birth	3 wks	at birth	3 wks	at birth	3 wks
Untreated	1	1.49	4.69	9.99	4.07	4.5	2.35	33.5	15.4
150 mg Fe per os	4	1.50	6.24	9.1	9.1	3.9	4.3	29.3	29.8
450 mg Fe per os	5	1.37	5.21	10.0	10.2	4.7	4.9	33.4	32.2
900 mg Fe per os	5	1.56	6.51	11.3	10.5	4.9	4.8	35.8	34.0
150 mg fer. fum.	4	1.52	6.00	10.0	5.6	4.5	3.2	32.3	22.0
450 mg fer. fum.	3	1.57	6.20	9.9	5.8	4.7	3.2	32.7	18.7
900 mg fer. fum.	1	1.58	6.42	10.9	6.7	4.3	4.5	35.0	21.0

The results in this table show that all piglets receiving ferrous fumarate, regardless of dosage, developed anaemia. No toxic symptoms were recorded in the groups receiving iron dextran even in the group whose dose was 990 mg Fe as iron dextran.

Example 8

The method was also tested on service litters, 150 mg iron as iron dextran per os being compared with the same amount given i.m. Treatment was effected 8—24 hours after birth on a total of 168 piglets. The following results were obtained:

TABLE IX

	Number of pigs	Wt.	No. of Pigs	Wt.	No. of Pigs	Hb	Rbl	Haem
		3 weeks		8 weeks				
i.m.	85	5.40	77	14.33	84	11.35	5.10	35.9
per os	83	5.70	78	14.10	82	10.44	4.84	33.3

This table shows that the piglets receiving iron dextran per os had a higher average weight at 3 weeks and that their haematological values are fully acceptable.

Example 9

120 piglets from the same farm were given 200 mg of iron orally, 20 to 25 piglets being used for each product. Split litters were not used. The products were administered approximately 6 to 8 hours after birth. The product and the Hb results are shown in Table X.

TABLE X

Product	Hb (Haldane Scale) 3 weeks	8 weeks
'Imposil' 10% Iron dextran	64	58
'Ferridex' Roseo-Iron dextran glycerol glycoside	59	55
'Ironex' Leo-hydrogenated iron dextran	58	53
'Iodofer' Ferrosan iron poly galactose (Crookes Labs.)	63	50
'Idozan' Ferrosan-colloidal ferric hydroxide (Idozan is a Registered Trade Mark)	48	46

Formulations for use in this invention are illustrated by the following Examples A to H in which recipes are given for unit doses 300 mg of iron dextran contain 100 mg iron. In these formulations the iron dextran may be replaced with any other suitable iron complex in solid, or, where appropriate, liquid form.

Example A

Tablet

Iron Dextran	900 mg
Acacia	40 mg
Water	q.s.
Potato Starch	100 mg
Magnesium Stearate	5 mg

Example B

Capsule

Iron Dextran	600 mg
Acacia	30 mg
Water	q.s.
Magnesium Stearate	3 mg

Example C

Pill

Iron Dextran	750 mg
Syrup of Liquid Glucose	a sufficient quantity to make a pill

Example D

Bolus

Iron Dextran	600 mg
Treacle with linseed meal	a sufficient quantity to make a pill

Example E

Paste

Iron Dextran	750 mg
Mucilage of tragacanth or acacia	A sufficient quantity to make a paste
Preservative (chlorocresol)	q.s.
Flavouring (Apple)	q.s.

Example F

Aerosol

Iron Dextran	900 mg
Sorbitan Mono-oleate	20 mg
Water soluble flavour	q.s.
Water to	2 ml
Dichlorodifluoro methane	0.5 ml
Trichloromonofluoro-methane	0.5 ml

Packed into can having valve which would deliver a metered dose into mouth of each piglet.

Example G

Wettable Powder

Iron Dextran	750 mg
Tween 80 (surfactant) (Tween is a Registered Trade Mark)	0.05% w/w
Sodium carboxymethyl cellulose	4% w/w
Flavouring	q.s.

This formulation readily disperses in water (total volume 2 ml) to form a drench.

WHAT WE CLAIM IS:—

1. A method for the prophylactic treatment of iron deficiency in piglets which comprises administering orally to the piglet within 24 hours of its birth a complex containing iron and a polysaccharide, a di-saccharide, a protein or a polypeptide.

2. A method according to Claim 1, wherein the complex contains a polysaccharide.

3. A method according to Claim 1, wherein the complex contains a dextran, dextrin, polyglucose, polymannose, polymaltose, polysucrose, polygalactose, mannan, galactan, levan, inulin, polyfructose, xylan, araban, an alginate, chrondroitin or pectin.

4. A method according to Claim 2 or Claim 3, wherein the end groups of the polysaccharide have been modified by hydrogenation, oxidation, heptonate formation or glycerol glycoside formation.

5. A method according to any one of the preceding claims wherein the complex is used in admixture with a non-toxic polyhydroxy compound or a non-toxic organic acid.

6. A method according to any of the preceding claims, wherein the complex is administered in admixture with another compound which is orally tolerated by the piglet.

7. A method according to Claim 6, wherein the other compound is an inert diluent, a piglet foodstuff, a physiologically desirable trace element, a vitamin, an antibiotic, an absorption aid, or an immunoglobulin.

8. A method according to Claim 7, wherein the diluent comprises water.

9. A method according to Claim 7, wherein the trace element comprises copper, cobalt, manganese or a mixture thereof.

10. A method according to Claim 7, wherein the vitamin comprises vitamin A, D, B_1, B_2, B_6, B_{12}, E (or another antioxidant) or a mixture thereof.

11. A method according to Claim 7, wherein the antibiotic is a broad spectrum antibiotic.

12. A method according to any one of the preceding claims, wherein the complex is administered to the piglet from 3 to 24 hours after birth.

13. A method according to Claim 12, wherein the administration takes place from 3 to 16 hours after birth.

14. A method according to Claim 12, wherein the administration takes place about 8 hours after birth.

15. A method according to any one of the preceding claims, wherein from 50 to 1,000 mg of iron are administered to the piglet.

16. A method according to Claim 15, wherein from 50 to 300 mg of iron are administered to the piglet.

17. A method according to Claim 16, wherein from 100 to and 250 mg of iron are administered to the piglet.

18. A method according to any one of the preceding claims, wherein a single dose of iron is administered to the piglet.

Example B

Capsule

Iron Dextran	600 mg
Acacia	30 mg
Water	q.s.
Magnesium Stearate	3 mg

Example C

Pill

Iron Dextran	750 mg
Syrup of Liquid Glucose	a sufficient quantity to make a pill

Example D

Bolus

Iron Dextran	600 mg
Treacle with linseed meal	a sufficient quantity to make a pill

Example E

Paste

Iron Dextran	750 mg
Mucilage of tragacanth or acacia	A sufficient quantity to make a paste
Preservative (chlorocresol)	q.s.
Flavouring (Apple)	q.s.

Example F

Aerosol

Iron Dextran	900 mg
Sorbitan Mono-oleate	20 mg
Water soluble flavour	q.s.
Water to	2 ml
Dichlorodifluoro methane	0.5 ml
Trichloromonofluoro-methane	0.5 ml

Packed into can having valve which would deliver a metered dose into mouth of each piglet.

Example G

Wettable Powder

Iron Dextran	750 mg
Tween 80 (surfactant) (Tween is a Registered Trade Mark)	0.05% w/w
Sodium carboxymethyl cellulose	4% w/w
Flavouring	q.s.

This formulation readily disperses in water (total volume 2 ml) to form a drench.

WHAT WE CLAIM IS:—

1. A method for the prophylactic treatment of iron deficiency in piglets which comprises administering orally to the piglet within 24 hours of its birth a complex containing iron and a polysaccharide, a di-saccharide, a protein or a polypeptide.

2. A method according to Claim 1, wherein the complex contains a polysaccharide.

3. A method according to Claim 1, wherein the complex contains a dextran, dextrin, polyglucose, polymannose, polymaltose, polysucrose, polygalactose, mannan, galactan, levan, inulin, polyfructose, xylan, araban, an alginate, chrondroitin or pectin.

4. A method according to Claim 2 or Claim 3, wherein the end groups of the polysaccharide have been modified by hydrogenation, oxidation, heptonate formation or glycerol glycoside formation.

5. A method according to any one of the preceding claims wherein the complex is used in admixture with a non-toxic polyhydroxy compound or a non-toxic organic acid.

6. A method according to any of the preceding claims, wherein the complex is administered in admixture with another compound which is orally tolerated by the piglet.

7. A method according to Claim 6, wherein the other compound is an inert diluent, a piglet foodstuff, a physiologically desirable trace element, a vitamin, an antibiotic, an absorption aid, or an immunoglobulin.

8. A method according to Claim 7, wherein the diluent comprises water.

9. A method according to Claim 7, wherein the trace element comprises copper, cobalt, manganese or a mixture thereof.

10. A method according to Claim 7, wherein the vitamin comprises vitamin A, D, B_1, B_2, B_6, B_{12}, E (or another antioxidant) or a mixture thereof.

11. A method according to Claim 7, wherein the antibiotic is a broad spectrum antibiotic.

12. A method according to any one of the preceding claims, wherein the complex is administered to the piglet from 3 to 24 hours after birth.

13. A method according to Claim 12, wherein the administration takes place from 3 to 16 hours after birth.

14. A method according to Claim 12, wherein the administration takes place about 8 hours after birth.

15. A method according to any one of the preceding claims, wherein from 50 to 1,000 mg of iron are administered to the piglet.

16. A method according to Claim 15, wherein from 50 to 300 mg of iron are administered to the piglet.

17. A method according to Claim 16, wherein from 100 to and 250 mg of iron are administered to the piglet.

18. A method according to any one of the preceding claims, wherein a single dose of iron is administered to the piglet.

* C L M S *

19. A method according to any one of the preceding claims, wherein a liquid or paste containing the complex is administered from a container adapted to deliver a metered dose.

20. A method according to claim 1 and substantially as hereinbefore described in any one of Examples 1 to 9.

21. A pig whenever treated by a method according to any one of the preceding claims.

22. A composition which is orally acceptable to the new born piglet, which comprises an iron-dextran, and a diluent, surface active agent, carrier, or other matter which is orally acceptable to the piglet, the composition being a solid or paste.

23. A composition according to Claim 22, the form of wettable powder, a tablet, a capsule, a pill, a bolus, or a paste.

24. A composition according to Claim 21 or 22 in a unit dosage form comprising from 50 to 1,000 mg of iron.

25. A composition according to Claim 24, comprising from 50 to 300 mg of iron.

26. A composition according to Claim 25, comprising from 100 to 250 mg of iron.

27. A composition according to Claim 22, comprising a paste contained in a bottle, gun or container adapted to eject a metered dose of its contents.

28. A composition according to Claim 22 and substantially as hereinbefore desoribed.

29. A composition according to Claim 22 and substantially as hereinbefore described in any one of Examples A to G.

30. A method according to any one of Claims 1 to 18 wherein the piglet is reared for at least 2 weeks after the treatment.

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