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Preclinical Evaluation of Novel All-in-one Formulations of 5-Fluorouracil and Folinic Acid with Reduced Toxicity Profiles - Supplementary Data

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Preclinical Evaluation of Novel All-in-one Formulations of 5-Fluorouracil and Folinic Acid with Reduced Toxicity Profiles - Supplementary Data

Abstract

Objectives: 5-Fluorouracil (5-FU) in combination with its synergistic biomodulator folinic acid maintains a pivotal position in cancer chemotherapy. However, clinical limitations persist with the administration of these drugs in combination including phlebitis and catheter blockages, which are associated with reduced efficacy and/or quality of life for patients. We have previously reported novel all-in-one, pH neutral, parenteral 5-FU and folinic acid formulations (termed Fluorodex) incorporating beta-cyclodextrins. Fluorodex maintains potency while overcoming the accepted incompatibility of 5-FU and folinic acid.

Methods: We performed toxicological, pharmacokinetic and biodistribution, and efficacy evaluations of Fluorodex compared to 5-FU:folinic acid using several administration routes and schedules in two rodent models. These were compared to dose-matched sequential administration of 5-FU:folinic acid.

Results: Fluorodex showed bioequivalence to 5-FU:folinic acid as assessed by tissue distribution and pharmacokinetics of 5-FU, but was generally better tolerated as determined by weight loss, hematological and other clinical parameters. Compared to 5-FU:folinic acid, Fluorodex was also associated with reduced phlebitis using a rabbit ear vein model. Furthermore, equivalent to enhanced efficacy of Fluorodex compared to 5-FU:folinic acid against human carcinoma tumour models in mice was observed.

Conclusions: These novel all-in-one formulations represent a superior injectable form of 5-FU that allows co-delivery of folinic acid. This should translate to improved patient tolerability with potential for enhanced efficacy.

Keywords

CMMB

Disciplines

Life Sciences | Physical Sciences and Mathematics | Social and Behavioral Sciences

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Supplementary Data

Table S1 Haematology parameters – male rats

	β-CD(HP) control			FD(HP)			5FU:FA		
	Mean	SD	N	Mean	SD	N	Mean	SD	N
WBC (x10⁹/L)	8.43	1.39	4	2.40	1.10	4	2.33	2.70	4
<i>Neutrophils</i>	1.08	0.30	4	0.95	1.70	4	1.45	2.70	4
<i>Lymphocytes</i>	7.03	1.03	4	1.35	0.68	4	0.90	0.54	4
<i>Monocytes</i>	0.23	0.10	4	0.10	0.00	4	0.10	0.00	4
<i>Eosinophils</i>	0.1	0.00	4	0.1	0.00	4	0.1	0.00	4
RBC (x10¹²/L)	6.79	0.28	4	6.30	1.73	4	5.29	1.95	4
Hgb (g/L)	144.00	4.69	4	135.00	35.52	4	116.00	44.58	4
Hct (L/L)	0.43	0.02	4	0.39	0.10	4	0.33	0.13	4
MCV (fL)	62.95	1.41	4	61.80	1.50	4	61.30	2.51	4
MCH (pg)	21.20	0.32	4	21.45	0.31	4	21.88	0.39	4
MCHC (g/L)	336.75	4.11	4	347.50	3.51	4	357.25	8.96	4
Plt (x10⁹/L)	1120.50	133.68	4	315.00	527.44	3	111.25	216.50	4

WBC: while blood cell; RBC: red blood cell; Hgb: hemoglobin; Hct: hematocrit; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; Plt: platelets.

Table S2 Haematology parameters – female rats

	β-CD(HP) control			FD(HP)			5FU:FA		
	Mean	SD	N	Mean	SD	N	Mean	SD	N
WBC (x10⁹/L)	5.95	0.70	4	2.30	0.69	4	1.10	0.35	4
<i>Neutrophils</i>	0.75	0.39	4	0.10	0.00	4	0.1	0.00	4
<i>Lymphocytes</i>	5.08	0.710	4	2.15	0.73	4	1.10	0.35	4
<i>Monocytes</i>	0.10	0.00	4	0.10	0.00	4	0.1	0.00	4
<i>Eosinophils</i>	0.10	0.00	4	0.1	0.00	4	0.1	0.00	4
RBC (x10¹²/L)	6.22	0.28	4	5.29	0.20	4	4.86	0.22	4
Hgb (g/L)	132.00	6.38	4	113.25	5.38	4	100.75	3.50	4
Hct (L/L)	0.39	0.01	4	0.31	0.01	4	0.29	0.01	4
MCV (fL)	62.60	1.89	4	57.93	0.92	4	59.60	0.66	4
MCH (pg)	21.23	0.83	4	21.48	0.33	4	20.78	0.76	4
MCHC (g/L)	339.00	6.22	4	370.50	4.43	4	348.25	9.18	4
Plt (x10⁹/L)	1049.50	92.31	4	44.50	16.84	4	3.25	4.50	4

WBC: while blood cell; RBC: red blood cell; Hgb: hemoglobin; Hct: hematocrit; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; Plt: platelets.