

Pharmacodynamics

Cumulative Drug Responses

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Objectives

- Understand the concepts of drug exposure
- Appreciate the difference between immediate action, delayed effect and cumulative response to a drug
- Describe the response to frusemide with different dosing schedules
- Appreciate the basis of schedule dependence of drug response e.g. in cancer chemotherapy

Terminology

- Drug Action
 - » on a receptor
- Drug Effect
 - » receptor mediated change in a physiological intermediate
- Drug Response
 - » observed consequence of physiological intermediate

Drug Exposure

- Response is related to drug exposure
- Exposure Indicators

Dose

- Single Dose
- Daily Dose Rate
- Cumulative Dose

Concentration

- Area under Time vs Conc Curve (AUC)
- Average Steady State Conc (C_{ss})
- Area under Time vs Effect Curve (AUC_e)

Acid Pump Inhibitors

- Gastric/Duodenal ulcers are dependent on acid secretion
- Acid Pump inhibitors block gastric acid secretion
 - » e.g. omeprazole
- Inhibition is due to irreversible binding

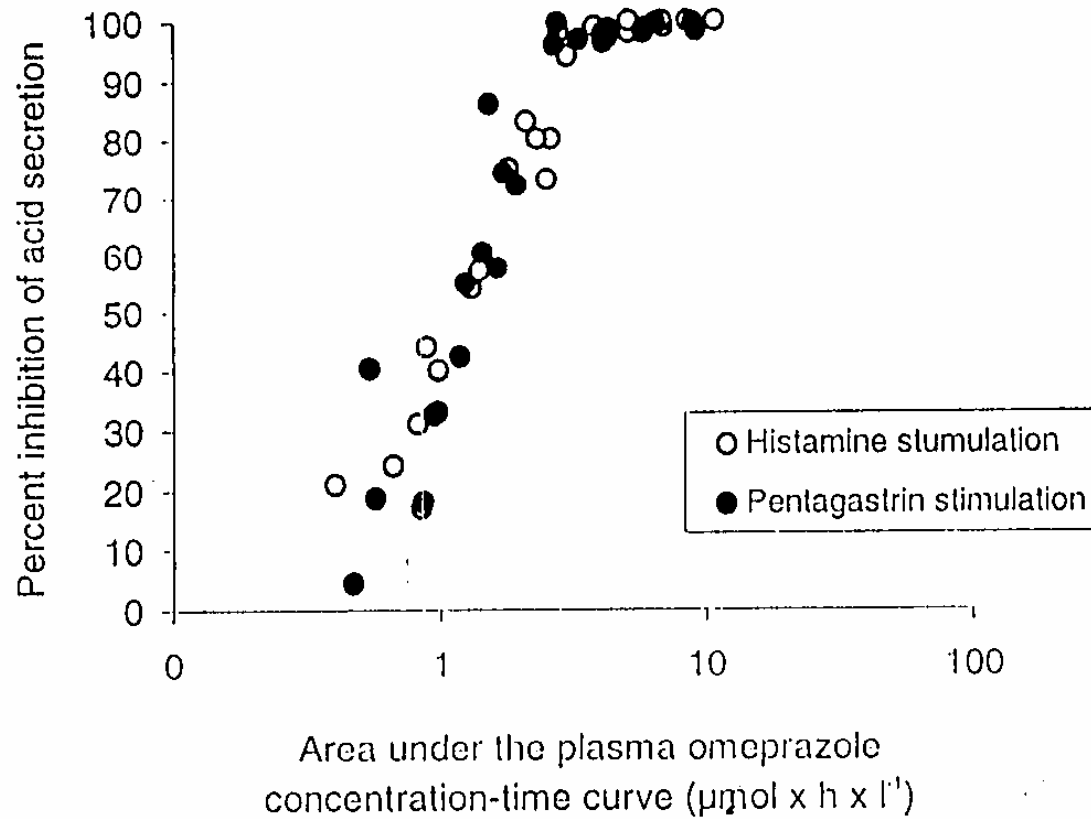
Acid Pump Inhibition

- Omeprazole is a prodrug
- Metabolised under acid conditions to a sulphenamide metabolite
- Sulphenamide forms a covalent disulphide bond with cysteine which is part of the acid pump
- Restoration of acid secretion depends on synthesis of new pump molecules

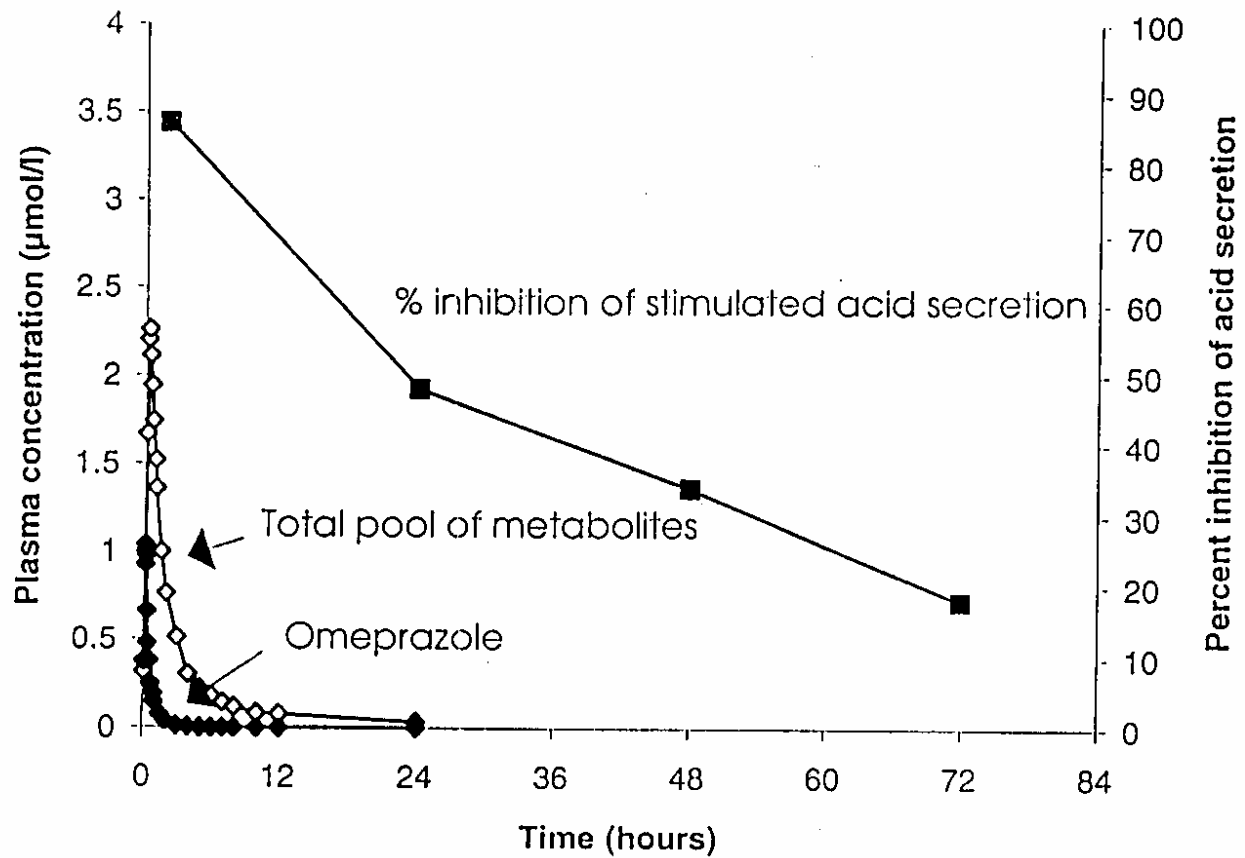
Acid Pump Inhibitors

- Action
 - » inhibition of gastric acid pump
- Effect
 - » decreased acid secretion and increased pH
- Response
 - » ulcer healing

Acid Pump Inhibition and AUC



Recovery of Acid Pump



Ulcer Healing Response

- Takes several weeks of acid inhibition to heal an ulcer
- Acid inhibition Effect is constant but the Response continues to develop (e.g. smaller size of ulcer)
- Response is proportional to AUC and independent of time course of omeprazole

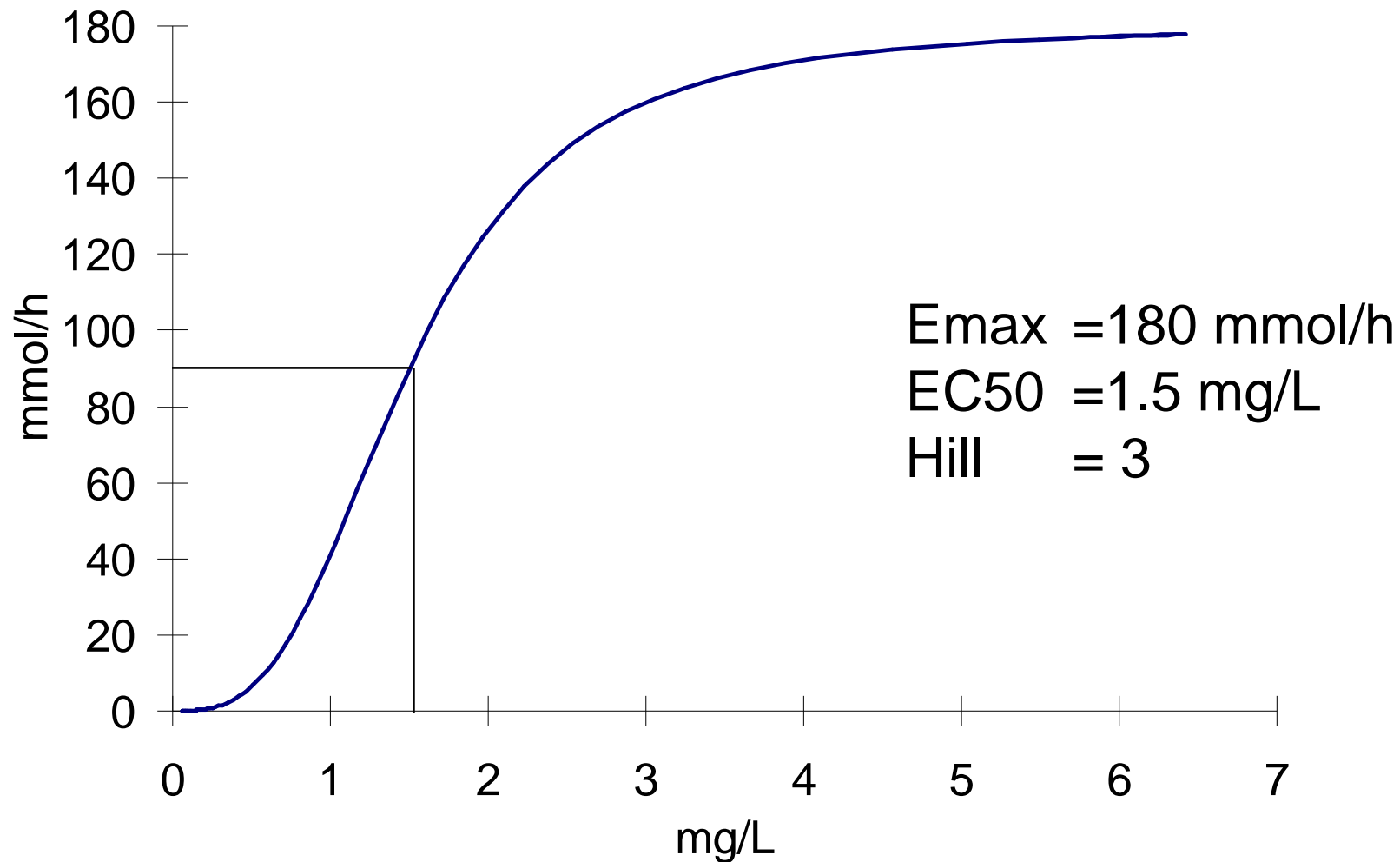
Diuretics and Heart Failure

- Digoxin, ACE inhibitors, beta blockers
 - » Used to improve survival
- Diuretics provide relief of symptoms
 - » Mainly produced by excess fluid
 - breathlessness, ankle swelling, (dropsy)
 - » Benefit is related to net reduction in fluid

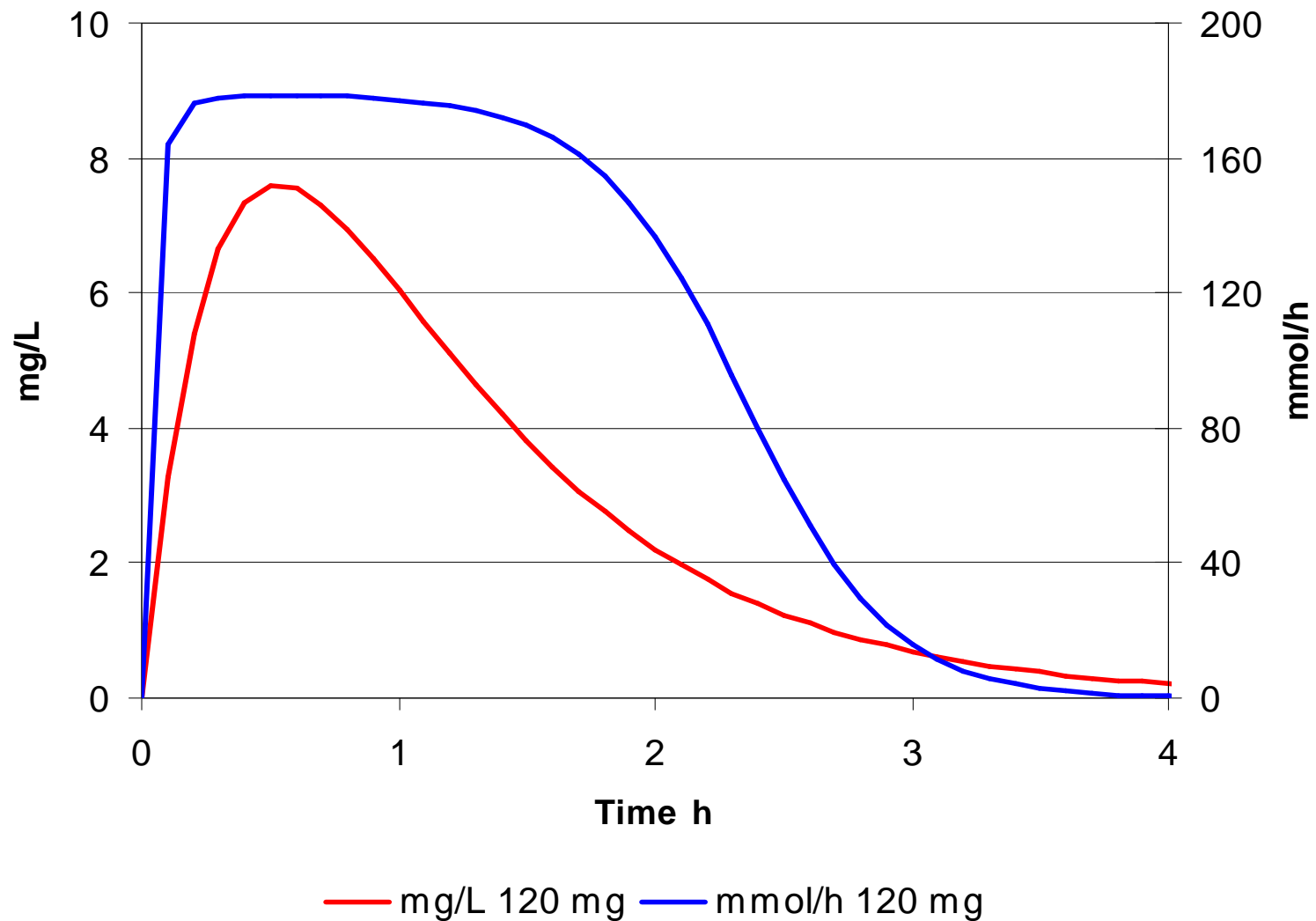
Diuretic Action/Effect/Response

- Diuretic Action
 - » Inhibition of Na⁺ reabsorption
- Diuretic Effect
 - » Increased Na⁺ and H₂O excretion
- Diuretic Response
 - » Cumulative fluid loss

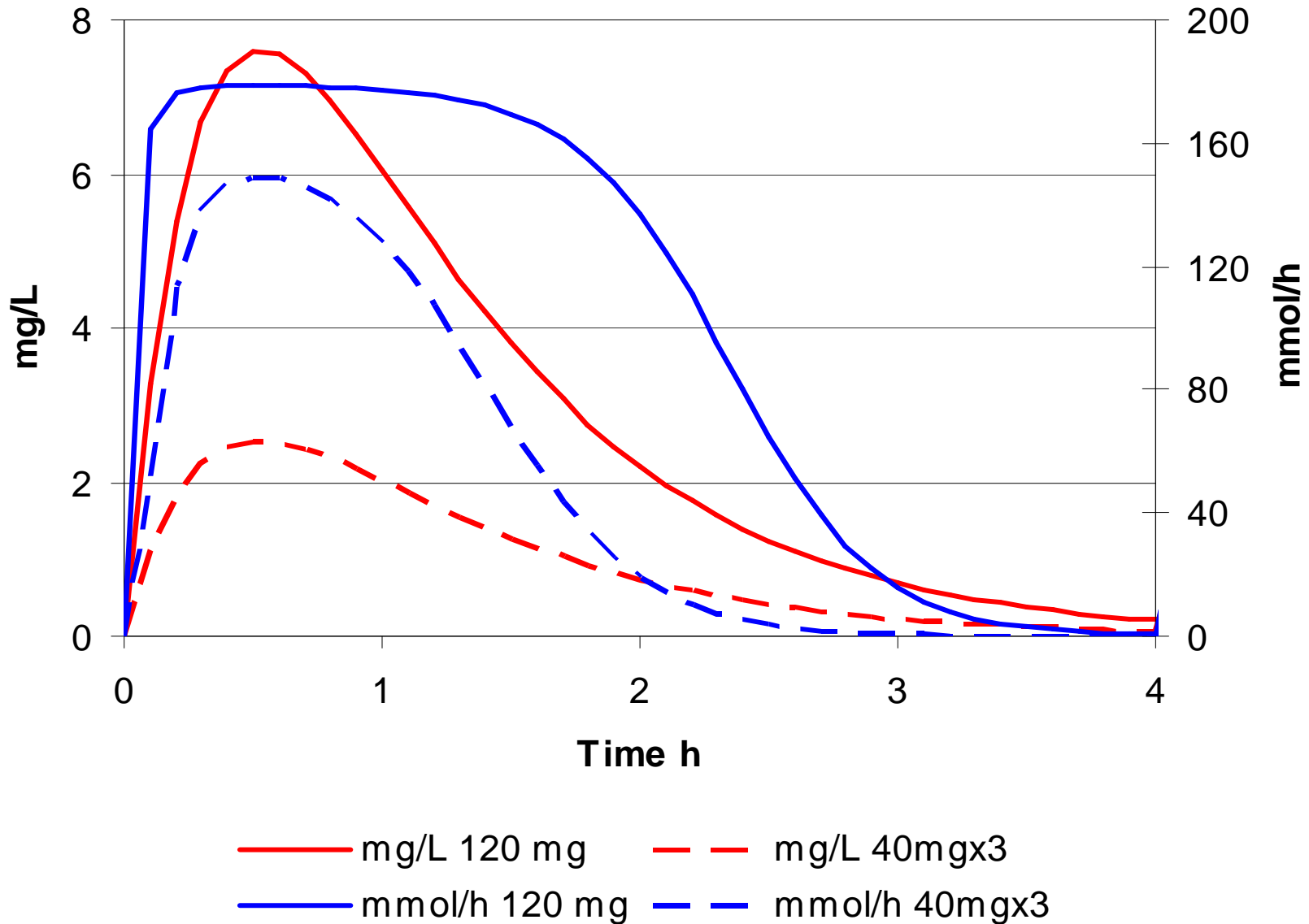
Frusemide Diuretic Effect



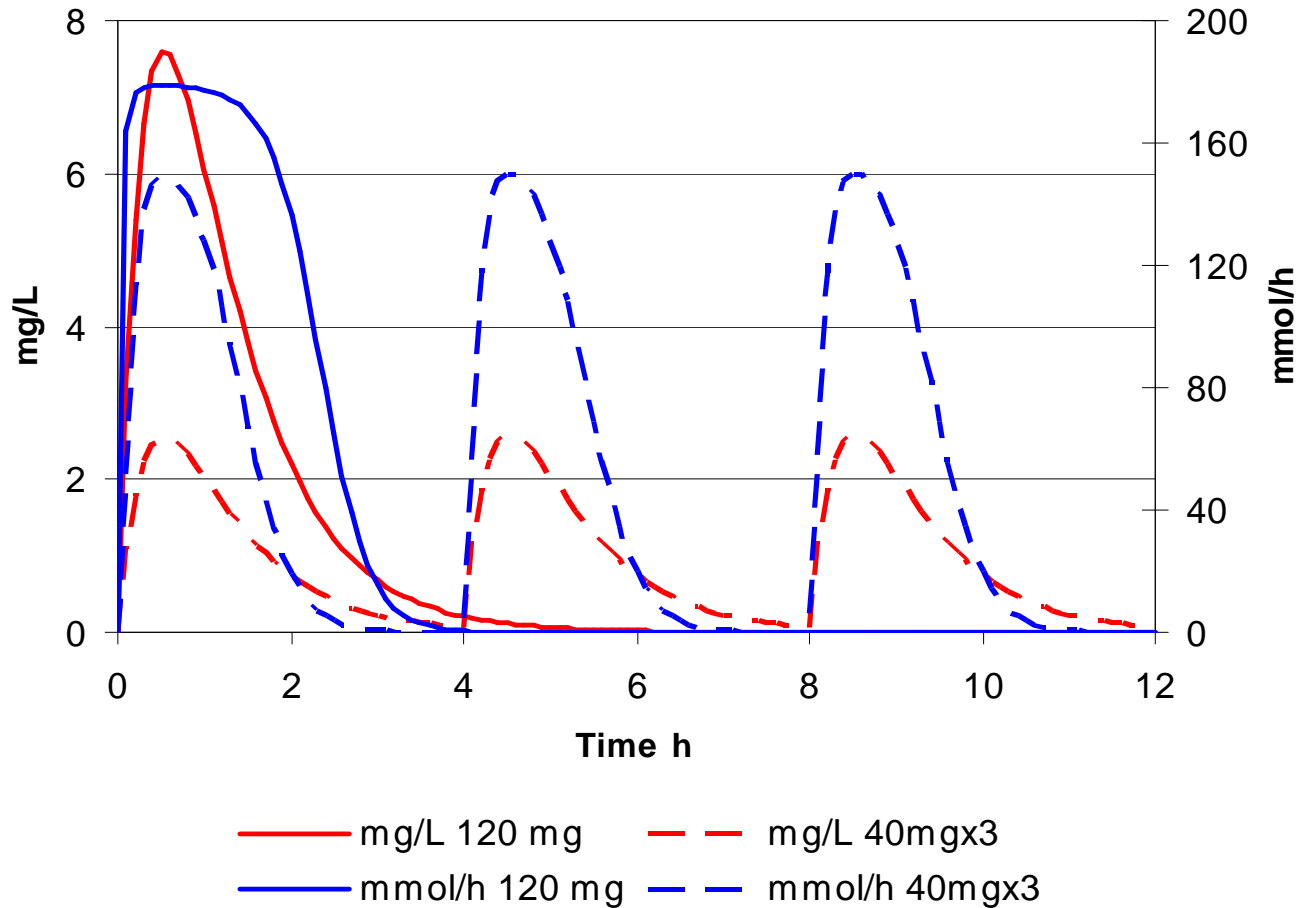
Frusemide Diuretic Effect



Frusemide 120 and 40 mg



Frusemide Response



40 mg x 3

» AUC_{0-12h} = 600 mmol
Na⁺/12h

120 mg x 1

» AUC_{0-12h} = 400 mmol
Na⁺/12h

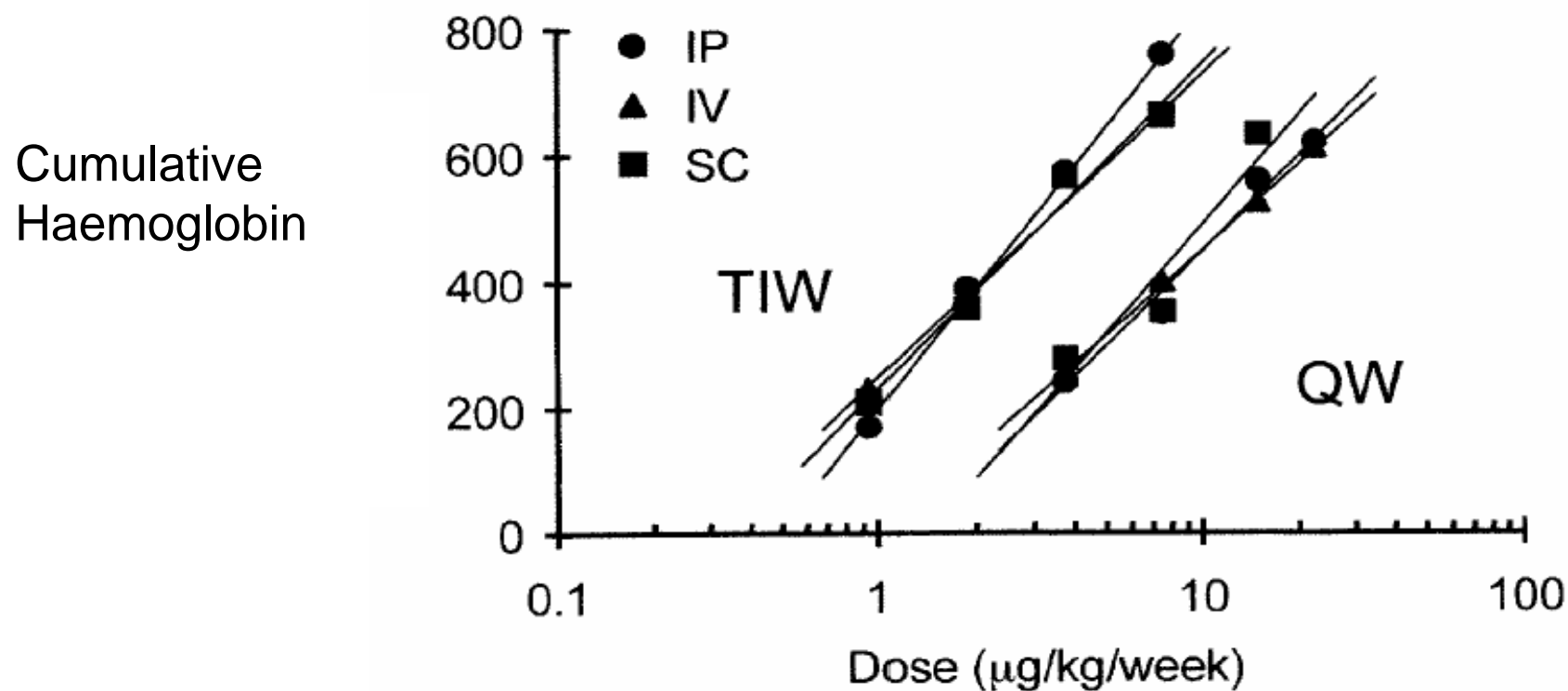
**Response is increased 50%
using 40 mg x 3**

Schedule Dependence

- Response is NOT proportional to cumulative diuretic dose or AUC
- Response IS proportional to cumulative diuretic effect or AUC_e
- Phenomenon is known as
 - » “Schedule Dependence”
 - » i.e. same dose but different response depending on dosing schedule

Darbepoetin Schedules

What does potency mean?



Egrie JC, Dwyer E, Browne JK, Hitz A, Lykos MA. Darbepoetin alfa has a longer circulating half-life and greater in vivo potency than recombinant human erythropoietin. *Experimental Hematology* 2003;31(4):290-9

Anti-Cancer Agents

- Alkylating agents
 - » Irreversible binding to cell components
 - » Schedule independent
 - E.g. carboplatin
- Anti-Metabolites
 - » Reversible effects on cell metabolism
 - » Schedule dependent
 - E.g. methotrexate

Anti-Cancer Agents

- Action
 - » Irreversible binding to cell structure
 - » Competition for metabolites
- Effect
 - » Block of cell division/cell death
- Response
 - » Slowing or reversal of tumour growth

Anti-Cancer Agents

- Schedule Dependence is common
- Large intermittent doses are often more toxic and less effective than smaller repeated doses
- Note: AUC may be used to guide individual treatment
 - » Evans et al. 1998

Evans W, Relling M, Rodman J, Crom W, Boyett J, Pui C. Conventional compared with individualized chemotherapy for childhood acute lymphoblastic leukemia. *New England Journal of Medicine* 1998;338:499-505.