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# Pharmacokinetics of Doxorubicin and Cisplatin after administration by Avitine/Omnipaque Gel applied directly to the liver

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15

**A report of an accidental overdose of chemotherapy in a patient receiving protracted venous infusion of 5-fluorouracil (PVI5FU) for gastroesophageal cancer**

Julie Watters, Marianne Taylor, Liz Mellor

**Key Content Words:** *Epirubicin; cisplatin; PVI5FU*

**Summary:** Gastroesophageal cancer is responsible for approximately 10,000 deaths per year in the UK. Systemic chemotherapy forms part of treatment with both curative and palliative intent.

There is no international gold standard regimen, but ECF (epirubicin; cisplatin; PVI5FU) is accepted as a reference regimen in the UK and Europe.<sup>1</sup>

At Cookridge Hospital PVI5FU is delivered to patients via the Walkmed<sup>®</sup> delivery system. Standard fill bags of undiluted 5FU 50 mg/ml are employed and patient dose is adjusted by setting the rate (in milliliters per hour) on the Walkmed<sup>®</sup> pump. The patients are connected to the pump and the 5FU infuses over a period of 21 days.

We report the case of a 66-year old male patient who accidentally received 10 g of 5FU over a period of up to 36 hours.

The patient attended the hospital for his fifth cycle of ECF. At discharge it was noted that the 5FU in the Walkmed<sup>®</sup> bag scheduled for infusion over 21 days had completely infused.

A literature search was conducted regarding treatment of overdose of 5FU, but this yielded very little information. The use of uridine<sup>2-5</sup> was considered; however, as this is not available as a pharmaceutical product in the UK, it was not used. The patient was treated symptomatically with a combination of allopurinol, growth factors, prophylactic antibiotics, anti-fungals, and antivirals.

The patient suffered severe mucositis, minor diarrhoea, and myelosuppression. He was discharged from hospital 19 days later after a complete recovery. Routine follow-up at 3 months post overdose has been unremarkable.

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16

**Possible potentiation of gynecomastia in a prostate cancer patient receiving hormonal ablation therapy as well as Highly Active Anti-Retroviral Therapy (HAART) for HIV infection — a case report**

Wayne Cottrell

**Key Content Words:** *Gynecomastia, prostate cancer, goserelin, HAART, stavudine, bicalutamide*

**Summary:** The patient, a 68-year old HIV-positive male, had been receiving triple anti-retroviral therapy consisting of lamivudine (3TC) 150 mg po bid, stavudine (d4T) 40 mg po bid, and efavirenz (Sustiva) 600 mg po qhs. He was subsequently diagnosed with T3 adenocarcinoma of the prostate in early 1999 (PSA 7.7, CD4 • 400) and accordingly received monthly goserelin 3.6-mg injections accompanied by flutamide 250 mg po tid, for the next 4 months. At the fourth visit, he complained of pronounced gynecomastia, breast tenderness bilaterally and increased abdominal girth. Two months later, he began a 6.5-week course of radiotherapy to the prostate, with a planned 3-year period of adjuvant hormonal therapy to follow (as per EORTC protocol guidelines). Two weeks into radiotherapy, the gynecomastia was as prominent (approximately a B cup bilaterally) and the flutamide and goserelin were stopped. These were, experimentally,

substituted with bicalutamide 150 mg daily. Throughout the following year, his PSA remained low (0.08–0.3), but his testosterone level had risen to the 12–14 range. As the gynecomastia remained essentially unchanged, he met with a plastic surgeon to consider reduction mammoplasty. This action was mutually decided against since it might recur with further treatment for prostate cancer; he was no longer symptomatic (when changed to bicalutamide), and the alteration of his appearance was acceptably concealed by loose-fitting clothes. In January 2001, his PSA yet remaining low, the LHRH agonist was reintroduced. Half a year later, all hormonal ablation was withdrawn. Clinical photographs, taken on three separate occasions during this 2 and 1/2-year period, show no regression of breast tissue or abdominal fat pad. Gynecomastia arises from alteration of the ratio of estrogens to androgens, the presence of testicular or adrenal neoplasms or the use of some medications (e.g., Spironolactone, cimetidine). 1) It has also been implicated in a syndrome of peripheral lipodystrophy in patients receiving HIV protease inhibitors. 2) Moreover, d4T (stavudine) alone has been associated, through temporal observation, with the development of gynecomastia. 3) Could this gentleman's profound gynecomastia have resulted from compounding testosterone suppression with other heretofore-unknown mechanisms? Until this is known, would it be prudent for HIV physicians to avoid prescribing stavudine, or incorporate a non-nucleoside analog rather than a protease inhibitor into HAART regimens for prostate cancer patients?

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17

## Case study: pharmacokinetics of doxorubicin and cisplatin after administration by avitene/omnipaque gel applied directly to the liver

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**Key Content Words:** *Doxorubicin, cisplatin*

**Purpose:** A pharmacokinetic analysis of doxorubicin and cisplatin was performed in order to determine the extent of systemic exposure after chemoembolisation. Verapamil was included in one treatment, in order to attempt to circumvent drug efflux by P-glycoprotein.

**Methods:** A 3-year old child with stage 4 hepatoblastoma/HCC was given three treatments of doxorubicin/cisplatin (15, 28, and 17 mg doxorubicin plus 50, 93, and 58 mg cisplatin, respectively) made up in a gel consisting of avitene and omnipaque which was injected directly into the liver, specifically into the blood vessels serving the tumour (treatments 1 and 2) or into the hepatic artery (treatment 3). The fourth treatment (14.4 mg doxorubicin plus 48 mg cisplatin injected into the tumour blood vessels) included 120 µg verapamil. Blood samples were taken at various intervals pre- and post-treatment.

**Results:** Peak plasma concentrations of doxorubicin were found to occur approximately 30 min after drug application. Peak concentrations were 116, 344, 1658, and 20 ng/ml for treatments 1–4, respectively, with corresponding AUCs of 36.3, 69.3, 98.4, and 4.2 µg/ml min.

The platinum pharmacokinetic analysis is ongoing, and these data will also be presented, together with a summary of the clinical response after follow-up.

**Conclusion:** Chemoembolisation of doxorubicin did not reduce the systemic exposure to doxorubicin in this hepatically impaired patient. The addition of verapamil to the formulation, however, appears to have a marked effect on the systemic concentrations of doxorubicin after chemoembolisation, with 17%  $C_{max}$  and 11.7% AUC being achieved. This may have beneficial effects on doxorubicin toxicity, particularly on the risk of long-term cardiotoxicity.

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