SYSTEMIC RESORPTION OF 5-FLUOROURACIL USED IN INFUSION FLUID DURING VITRECTOMY

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SUMMARY:

PURPOSE: The aim of this study is to determine whether 5-fluorouracil (5FU) used in the infusion fluid during vitrectomy is systemically absorbed.

PATIENTS AND METHODS: The major catabolite of 5FU, α-fluoro-β-alanine (FBAL) was measured in urine samples of 2 patients that underwent vitrectomy using 5FU in the infusion fluid.

RESULTS: In both patients, FBAL was found in the urine samples collected up to 48 hours after the surgery, with the highest concentration and total amount in the first 6 hours after the first urine production after surgery. Moreover, the concentration and total amount of FBAL was higher in the patient who received silicone oil tamponade (versus 12.5% SF_6), with the longest surgery time (40 min versus 20 min) and the highest amount of infusion fluid used (350 ml versus 250 ml).

CONCLUSIONS: 5FU, used to prevent the formation of proliferative vitreoretinopathy (PVR), is systemically absorbed when used in infusion fluid during vitrectomy. As such, patient selection is needed to avoid adverse effects on procreativity. Further studies will be needed to determine which clinical setting will influence most the absorption.

RÉSUMÉ:

OBJECTIFS: Le but de cette étude est d'apprécier si le 5-fluoro-uracile (5FU), employé dans le liquide d'infusion durant la vitrectomie, est absorbé systémiquement.

PATIENTS ET METHODES: Alpha-fluoro-β-alanine (FBAL), le catabolite principal du 5FU, a été mesuré dans l'urine de 2 patients, ayant subi une vitrectomie, avec emploi de 5FU dans le liquide d'infusion.

RESULTATS: Chez les 2 patients, le FBAL a été mesuré dans l'urine jusqu'à 48 heures après l'opération, avec la plus haute concentration et quantité totale de FBAL dans les 6 premières heures après la première miction. En outre, la plus haute concentration et la plus grande quantité totale de FBAL a été mesurée après tamponnement interne par huile de silicone (versus 12.5% SF_6), après la chirurgie de longue durée (40 min versus 20 min) et après emploi d'une grande quantité de liquide de vitrectomie (350 ml versus 250 ml).

CONCLUSIONS: Le 5FU, ajouté dans le liquide de perfusion lors de la vitrectomie dans le but de prévenir la prolifération vitréorétinienne (PVR), est absorbé systémiquement. Pour cette raison, une sélection des patients s'impose afin d'éviter des effets secondaires, par example sur la reproduction. Toutefois, l'influence des paramètres opératoires nécessite des études supplémentaires.

SAMENVATTING:

DOEL: Het doel van deze studie is bepalen of 5-fluorouracil (5FU), gebruikt in de infusievloeistof tijdens vitrectomie, systemisch wordt geabsorbeerd.

MATERIAAL EN METHODE: Alfa-fluoro-β-alanine, de belangrijkste kataboliet van 5 FU, werd gemeten in de urine van 2 patiënten die een vitrectomie ondergingen waarbij 5FU in de vitrectomievloeistof werd gebruikt.

RESULTATEN: FBAL werd teruggevonden in de urine van beide patiënten tot 48 uur na beëindigen van de ingreep, met de hoogste concentratie en grootste absolute hoeveelheid in de eerste 6 uur na de eerste urine productie na de ingreep. Daarenboven was de hoogste concentratie en grootste absolute hoeveelheid FBAL geassocieerd met het gebruik van siliconenolie voor interne tamponnade (versus 12.5% SF_6), met de langste duur van heelkundig ingrijpen (40 min versus 20 min) en met de grootste hoeveelheid gebruikte vitrectomievloeistof (350 ml versus 250 ml).

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BESLUIT: 5FU, gebruikt ter preventie van proliferatieve vitreoretinopathie (PVR), wordt systemisch opgenomen indien toegevoegd aan de infusievloeistof tijdens vitrectomie. Patiëntenselectie is dus noodzakelijk om nevenwerkingen op de voortplanting te voorkomen. Verdere studies zijn noodzakelijk om te bepalen in welke klinische setting de absorptie het grootst is.

KEY WORDS:

5-fluorouracil, vitrectomy, proliferative vitreoretinopathy, systemic absorption, side-effects, reproduction

MOTS-CLÉS:

5-fluoro-uracile, vitrectomie, prolifération vitréorétinienne, absorption systémique, effets secondaires, reproduction

INTRODUCTION

Despite improved anatomical results with advanced vitreoretinal surgical techniques, proliferative vitreoretinopathy (PVR) remains the leading cause of failure of retinal surgery (2).
PVR is not a specific clinical entity, but rather the end result of anomalous wound healing, characterized by cellular migration and proliferation on both surfaces of the detached neuroretina, and within the vitreous base resulting in the formation of periretinal membranes.
Several studies have evaluated the efficacy of different drugs in the control of PVR. The agents commonly used in the pharmacological manipulation of the wound-healing response are antimetabolites, collagen inhibitors, steroids, nonsteroidal anti-inflammatory drugs and colchicine. Other substances such as endotoxins, peptides or conjugated drugs have been used experimentally. However, 5-fluoro-uracil (5FU) is the most extensively studied antiproliferative agent that has been used in humans, with a proven efficacy in the inhibition of proliferation of the retinal pigment epithelium (ID_{50} of 0.39 μg/ml) and in the prevention of PVR.
First synthesized in 1957, 5FU is a synthetic pyrimidine analog, formed by the substitution of a fluorine atom for a hydrogen atom at position 5 of the uracil ring (6).
The availability of 5FU for anabolism is determined by the extent of its catabolism. FBAL is the major metabolite of 5FU as 60 to 90% of systemically administered 5FU is excreted in the urine as FBAL (3). Urinary excretion eliminates 5 to 20% of the unmetabolised drug and biliary excretion accounts for 2-3% of total administered dose.
Studies showed that 5FU is effective in reducing the rate of PVR and tractional retinal detachment by 50%, from 26 % in the control group to 13% in the treatment group (2). No treatment related side effects were identified. Nevertheless, the positive effect of this peri operative infusion on the success rate of surgery for established PVR has not been proven. Toxicity studies using intravitreal injections of 5FU produced no changes in the rabbit retina, nor corneal toxicity (4).
Although the side effects of 5FU are numerous and well established, presently, no data are available on the systemic absorption of 5FU

given as a peroperative infusion and the possible influence of intravitreal 5FU on procreativity. Since 60-90% of administered dose is quickly excreted in urine as α-fluoro-β-alanine (FBAL) (3), we measured the amount of FBAL in the urine during 72 hours postoperatively, to determine whether intravitreally administrated 5FU is systemically absorbed.

PATIENTS AND METHODS

Two patients were included in this study. A standard 3-port pars plana vitrectomy was performed, using intravitreal infusion fluid with 5FU (200 μg/ml) and LMWH (8IU/ml). The volume of vitrectomy fluid used was recorded. The local Ethics Committee approved the study. All patients gave written informed consent according to institutional guidelines.
The first patient underwent a vitrectomy to remove silicone oil, used in previous surgery. The infusion lasted 20 minutes and 250ml infusion fluid was used. Internal tamponade was achieved using sulphur hexafluoride (12.5% SF_6). The patient was already pseudophakic. The second patient underwent a vitrectomy for a longstanding retinal detachment. The intervention took 40 minutes and 350ml infusion fluid was used. Silicone oil was used for internal tamponade. Cataract surgery was performed at the time of the vitrectomy.
Urine samples were collected after surgery. The first sample of urine was taken from the first urine produced after surgery. Afterwards, urine was collected in two 6-h fractions, one 12-h fraction and two 24-h fractions. All urine was kept refrigerated during collection and aliquots were frozen and stored at -20°C until transportation on dry ice at -80°C to the lab of Exposure Control in the Netherlands.
The sample preparation procedure and analysis were performed by gas chromatography-mass spectrometric analysis (GC-MSMS), as described previously by Sessink et al. (9). The detection limit for FBAL in urine was 6 μg/l.

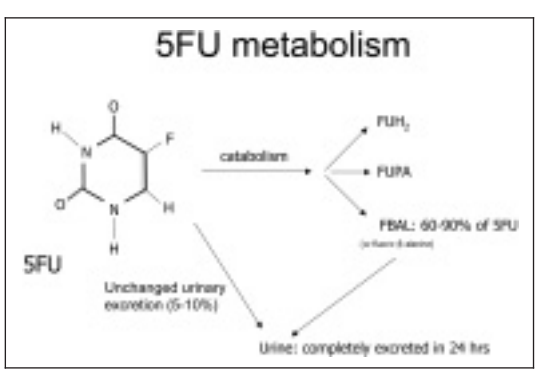

Figure 1: Molecular structure of 5-fluorouracil and its catabolic pathway.

RESULTS

The volume of urine, concentration of FBAL and total amount of FBAL in each urine sample of both patients are shown in Table 1.
The total amount of FBAL found in the urine during 72 hours postoperatively was 79.04μg in the patient with a gas tamponade . In the patient with silicone oil tamponade, the total excretion of FBAL was 7 times higher. In both patients, the amount of FBAL found in the urine was the highest in the first urine production after surgery and during the first 6 hours after this first urine production, irrespective of the type of tamponade. Eigthy three percent of FBAL was found in the first 6 hours urine production for the patient who had gas tamponade and 80% for the patient who had oil tamponade. In the urine of either patient collected 72 hours after surgery, FBAL could not be detected.

DISCUSSION

Although initially developed for the treatment of colorectal cancer, the spectrum of clinical use for 5FU has increased considerably, comprising nowadays indications such as head and neck cancer, lung cancer and breast cancer (5). Moreover, 5FU is also considered to be beneficial for the treatment of ocular scarring disorders, including cicatricial closure of filtration blebs following glaucoma surgery and PVR (1). The side effects of 5FU are numerous: hematologic, cardiovascular, neurologic, endocrine, metabolic, gastrointestinal, hepatic, dermatologic, respiratory, allergic, psychiatric, and ocular side-effects have been described (6).
As 5FU is a chemotherapeutic agent, consequences for the reproductive system must be considered (7).

Although 5FU has not been studied extensively in humans to permit an evaluation of its effects on fertility and general reproductive performance, all compounds which interfere with DNA, RNA and protein synthesis, may have an adverse effect on gametogenesis.

Animal studies with 5FU have been shown to induce chromosomal aberrations, changes in chromosomal organization of spermatogonia and inhibition of spermatogonial differentiation, resulting in transient infertility in rats. When 5FU is used in conventional regimens in humans, it causes only a minor reduction, if any, in sperm count, that is fully recoverable (8).

5FU has been shown to cross the placenta, enter into fetal circulation and be highly teratogenic in animal models. Stephens et al. (12) have reported multiple congenital anomalies with first-trimester exposure. It is not known whether fluorouracil is excreted in human milk. Because 5FU inhibits DNA, RNA and protein synthesis, mothers should not nurse while receiving this drug.

Although the systemic side effects of 5FU are well established, no report has been made of systemic toxicity that may occur from its intraocular use. The principal aim of this study was to determine whether 5FU used in infusion fluid during vitrectomy is systemically absorbed. No control group of patients has been examined as FBAL is a foreign amino acid because of his fluorine atom on the uracil ring (10).

FBAL, the major metabolite of 5FU, was found in the urine of both patients who underwent a vitrectomy, irrespective of the nature of intravitreal tamponade. Therefore, although the total dose of 5FU used is extremely small compared to the dosages used in chemotherapy and although the amount of FBAL in the urine is relatively small, 5FU is systemically absorbed and systemic side effects can not be excluded. Studies in the Netherlands suggest that nurses working in the oncology department, involved in administration of 5FU, have a higher risk for spontaneous abortion, low birth weight and congenital anomalies, but it is unknown to what extent these workers are really exposed. Therefore, from the results of this study, it cannot be concluded whether intravitreal infusion with 5FU may influence procreativity.

The total amount of FBAL in the urine in the patient with silicone tamponade is 7.15 higher than in the patient with the gas tamponade. The fact that surgery in the patient with silicone oil tamponade lasted twice as long as in the patient with gas tamponade (40 min versus 20 min) and took 350 ml infusion fluid compared to 250 ml can not be the only explanation for this difference.

The amount of FBAL is the highest (80%) in the first postoperative urine and during the first 6 hours after surgery, irrespective of the tam-

Table 1:

Patient	Time sampling	Sample	Volume (ml)	FBAL (ng/ml urine)	FBAL (μg)
1	04.15 pm	1	580	48.88	28.35
	04.15 - 10.15 pm	2	625	60.40	37.75
	10.15 pm - 4.15 am	3	600	13.08	7.85
	4.15 am - 4.15 pm	4	540	9.43	5.09
	4.15 am (24h)	5	600	ND	
	4.15 am (24h)	6	500	ND	
2	6.15 pm	1	800	565.69	452.55
	6.15 pm - 0.15 am	2	*		
	0.15 - 6.15 am	3	750	134.28	100.71
	6.15 am - 6.15 pm	4	850	6.35	5.40
	6.15 pm	5	1300	5.39	7.01
	6.15 pm	6	1000	ND	

Legend: FBAL: α-fluoro-β-alanine
ND: non detectable (FBAL < 5 ng/ml urine)
**: no urine produced during those 6 hours*

ponade. In the sample collected 72 hours postoperatively, FBAL was not detected in the urine of either patient.

Patient selection when using 5FU during a vitrectomy remains very important to avoid adverse effects on procreativity. Using this drug may be avoided in children, procreative patients and breastfeeding women. Further studies will be needed to determine in which clinical setting the absorption is the highest.

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