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# Estimation of irrigant absorption during transurethral resection of the prostate

## Assessment of fluorescein as a marker

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**Summary.** Absorption of irrigating solution may complicate transurethral resection of the prostate (TURP), and a system which warns of fluid overload reliably would be of benefit in the prevention of these complications. Fluorescein can easily be detected at very low concentrations in blood and can be added to the irrigating solution in amounts invisible to the naked eye, providing a possible means of easily monitoring the absorption of irrigant solution during TURP. To test this hypothesis, the plasma concentration of fluorescein was determined at intervals after intraperitoneal injection in rats. Although the published data on fluorescein suggest that it meets the criteria for a suitable marker substance to be introduced into the irrigant solution, the results show that plasma fluorescein is constant and not dose related. The addition of fluorescein to the irrigant solution would not provide a quantitative means of determining the volume of irrigant absorbed. The use of other substances may provide the answer to this major clinical problem. We have defined a set of criteria which such a substance should fulfil.

**Key words:** Fluorescein - TURP - Prostatectomy - Irrigant absorption - Irrigating solution

Although transurethral resection of the prostate (TURP) remains the best treatment currently available for the relief of bladder outflow obstruction [3], absorption of irrigant during transurethral resection can still cause serious clinical problems [12, 16]. In addition, there is increasing evidence that significant haemodynamic changes occur during TURP [5] and that irrigating fluid absorption may be implicated in subclinical myocardial infarction after TURP [4].

A simple method for measuring absorption of irrigant rapidly and reliably during surgery would be of great benefit as an early warning system so that steps might be taken to eliminate or modify the consequences of absorption. An obvious method is to introduce a suitable marker substance into the irrigation solution, and then determine the blood concentration at intervals as an index of body burden, allowing estimation of the total amount absorbed.

Fluorescein is one of the few compounds licensed for use in humans without a specific pharmacological effect. It can be detected fluorimetrically at concentrations as low as 0.05 pmol/ml, and addition of sufficient fluorescein to give this plasma concentration after absorption of 100 ml of irrigating solution will not affect the clarity of the solution.

Sterile solutions of fluorescein for injection are available and are used to measure circulation time [8, 11]. Pharmacokinetic data suggest that the plasma concentration of fluorescein (and its major metabolite, fluorescein glucuronide) decays slowly and at a constant rate [1]. Hence, measurement of total plasma concentration of fluorescein peroperatively should reflect the total body burden without the need to extrapolate from decay curves.

An animal experiment was therefore designed to determine whether measurement of plasma concentrations of fluorescein and fluorescein glucuronide would permit determination of total body burden, prior to a clinical study.

## Materials and methods

Male Wistar rats weighing 300–330 g were anaesthetized with Hypnorm (Janssen Animal Health; fentanyl citrate 0.315 mg/ml + fluanisone 10 mg/ml, 1 ml/kg body weight by intramuscular injection), and were then given an intraperitoneal injection of fluorescein dissolved in 1 ml 0.15 mol/l saline over the range of concentrations shown in Table 1. These concentrations were chosen to reflect potential levels following TURP, based on published reports of fluid absorption during TURP [7, 14].

At intervals for 100 min after this injection, 0.3-ml samples of blood were withdrawn by direct cardiac puncture, transferred to heparinised tubes and centrifuged at 2,000 *g* for 10 min. One hundred microlitres of plasma was incubated with 20 units of β-glucuronidase from *Helix pomatia* [EC 3.2.1.31, Sigma (London) Chemical Co., Poole, Dorset UK] in 100 µl water, for 30 min at 37°C, in order to hydrolyse fluorescein glucuronide. Two millilitres of 0.1 mol/l sodium phosphate buffer, pH 7.4, was then added to each

**Table 1.** Plasma concentrations of (fluorescein + fluorescein glucuronide) after intraperitoneal injection in the rat

| Dose of fluorescein in rat | | Time after injection (min) | | | | | |
|---|---|---|---|---|---|---|---|
| | | 10 | 20 | 40 | 60 | 80 | 100 |
| ng/rat | nmol/kg body wt | pmol/ml in plasma | | | | | |
| 125 | 1.10 | 34.3 | 34.0 | 27.6 | 42.8 | 33.2 | 34.0 |
| 500 | 4.25 | 45.2 | 47.0 | 42.5 | 42.5 | 42.5 | 34.8 |
| 2000 | 16.98 | 33.5 | 30.3 | 39.6 | 34.8 | 33.2 | 34.8 |

**Table 2.** Tissue concentrations of fluorescein 100 min after intraperitoneal injection of 17 nmol/kg body weight in a male rat

| | pmol/g tissue |
|---|---|
| Kidney | 115 |
| Liver | 72.3 |
| Prostate | 64.1 |
| Pancreas | 16.5 |
| Lung | 11.2 |
| Epididymal fat pad | 10.4 |
| Brain | 5.3 |
| Spleen | 5.3 |
| Skeletal muscle | 5.3 |

sample, and the fluorescence at 505 nm (activation at 475 nm) determined using an Aminco-Bowman spectrophotofluorimeter (Silver Spring, Md., USA).

The animals remained deeply anaesthetized throughout the procedure, and were then killed. Tissues from the animal that had received the highest dose of fluorescein were dissected out (see Table 2) and were homogenized in 1 ml water/g tissue using a Polytron tissue emulsifier. Then 0.5 ml of each homogenate was incubated with 20 units of β-glucuronidase, as described above; samples were then deproteinized with 0.5 ml of 3 mol/l perchloric acid and cetrifuged at 2,000 *g* for 10 min. The resultant supernatant fraction was neutralized with 3 mol/l potassium hydroxide and cooled at 4°C to precipitate potassium perchlorate, which was removed by centrifugation. Aliquots (0.1 ml) of the supernatant fraction were mixed with 2 ml of 0.1 mol/l sodium phosphate buffer, pH 7.4, and the fluorescence determined as described above.

## Results

Table 1 shows that the plasma concentration of (fluorescein + fluorescein glucuronide) was indeed constant over a period of 100 min after injection, as was expected from the published pharmacokinetic data [1]. However, there was no dose-related difference in the plasma concentration of total fluorescein over the 16-fold range of doses administered, suggesting that fluorescein may be sequestered in tissues, then released back into the circulation over a prolonged period of time.

Table 2 shows that there was significant retention of fluorescein in a number of tissues, with a marked accumulation in the liver, kidney and prostate.

## Discussion

At present there is no simple and accurate method of quantifying irrigant absorption during TURP. The TUR syndrome is a continuing and significant complication of TURP and interest in the significance of irrigating fluid absorption has been reawakened by papers suggesting that there is an increased mortality associated with TURP in the longer term, compared to open prostatectomy [17, 19] - possibly due to subclinical myocardial infarction provoked by fluid and electrolyte shifts [4]. With the advent of transcervical resection of the endometrium, complications from irrigant absorption are also beginning to be seen in gynaecological practice.

A number of techniques have been reported for estimating the volume of irrigant absorbed during TURP. These include weighing the patient [6], measuring the amount of "lost" irrigating solution [10] or estimating concentrations of solutes added to the irrigant [14]. Other studies have used radio-isotopes to estimate the amounts absorbed [15] or related changes in serum sodium to absorption [18]. However, none of these methods has found favour in urological practice: in some instances the methods are unreliable or clearly impracticable for routine use and in others the assays are time consuming and laborious. Recently, ethanol has been added to the irrigant and concentrations of expired ethanol used to calculate absorption [9]. However, as a metabolically active compound, ethanol fails to meet the criterion for an ideal irrigating solution, first defined by Nesbit and Glickman in 1948 [13].

We have defined a set of criteria that any substance used to monitor absorption should fulfil:

1. It must be non-toxic, preferably metabolically inactive, and approved for parenteral administration to patients.
2. It must be distributed reproducibly in either plasma or total body water, with a low and constant rate of clearance and metabolism.
3. It must be colourless and undetectable in the irrigation fluid, so as not to obscure the operating field.
4. It must be readily measurable in low concentrations, by a simple and rapid technique.
5. It should be relatively inexpensive, since the majority will be "wasted".

The published data on fluorescein suggest that it meets the criteria for a suitable marker substance to be introduced

into the irrigant solution. The addition of fluorescein to the irrigant initially appeared to be an ideal solution, surmounting the problems which may arise when ethanol is used.

However, this study demonstrates that fluorescein would be useless as an indicator of the amount of irrigating fluid absorbed during transurethral resection, as it clearly fails the second of our criteria. These results were unexpected, as the uptake and steady re-release of fluorescein from the tissues has not been reported previously.

The use of an animal model allowed rapid evaluation without the complications attendant upon a clinical study. Intraperitoneal injection of the fluorescein solution in the rat was chosen, as it mimics the major route of absorption of irrigating solution following TURP [7, 15], and studies have shown that labelled glycine introduced into the peritoneal cavity during TURP may appear after 15 min [10].

We were limited to consideration of previously approved compounds, almost all of which have (by definition) distinct pharmacological effects. It is possible that other dyes may not exhibit the same behaviour and could be used, although few have the intense fluorescence of fluorescein itself.

The marked fluorescence of the prostate in comparison to other tissues following intraperitoneal injection was also surprising. Chang and Young [2] have proposed the use of a computer-monitored resectoscope to monitor capsular breaches by virtue of differences in electrical conductivity: it is possible that fluorescein might be used in an analogous manner to show when the capsule had been reached or as an indicator of residual protatic tissue during resection.

Although fluorescein is not suitable as a marker substance, there remains a requirement for a simple method of measuring irrigant absorption during TURP. It is possible that further advances based on this approach may succeed in providing a solution to this problem. A laboratory-based approach to the initial evaluation of any potential substances would seem prudent.

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