Extraction fraction at any urine flow and extraction percentage[1]

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Summary. Extraction fraction of renal solutes is ordinarily calculated as a ratio of arterial and venous concentration differences. Calculations provided in the present manuscript illustrate the need to correct for changes in renal venous concentration when solute extraction is low and urine flow simultaneously high.

The extraction fraction used by renal physiologists in the estimate of renal plasma flow, perfusion of functional mass, and percentage of plasma flow filtered is found in standard texts of renal physiology[2–5]. By definition extraction fraction has been calculated as arterial and venous concentration differences of any solute used to measure flow rate. Thus

$$Ex = \frac{Ax - Vx}{Ax} 100$$

where E is extraction, A the arterial and V the venous concentrations of solute x. This calculation assumes that venous outflow equals arterial inflow. Our calculations reveal that this assumption is true only when extraction of a solute is high and when urine flow is simultaneously minimal.

Calculations: By our definition

Ax = renal arterial concentration, mg/ml
Vx = renal venous concentration, mg/ml
Ux = urinary concentration, mg/ml
Ra = renal arterial flow, ml/min
Rv = renal venous flow, ml/min
Ru = urinary flow, ml/min

The amount of solute entering the kidney must equal the amount in renal venous blood plus the amount in urine.

$$Ax \cdot Ra = Vx \cdot Rv + Ux \cdot Ru \quad (1)$$

In addition, volume flow in the renal artery must equal total outflow, the sum of renal venous and urine flow + lymph

$$Ra = Rv + Ru \text{ or } Rv = Ra - Ru \quad (2)$$

Substituting in the first equation

$$Ax \cdot Ra = Vx\,(Ra - Ru) + Ux \cdot Ru \quad (3)$$

and re-arranging

$$Ax \cdot Ra - Vx\,(Ra - Ru) = Ux \cdot Ru \quad (4)$$

$Ux \cdot Ru$ is the amount of solute x excreted per unit time. Dividing both sides by the amount entering the renal artery

$$\frac{Ux \cdot Ru}{Ax \cdot Ra} = \frac{Ax \cdot Ra - Vx\,(Ra - Ru)}{Ax \cdot Ra} \quad (5)$$

If E is the fraction of solute X which is excreted

$$E = \frac{Ux \cdot Ru}{Ax \cdot Ra} = \frac{Ax - Vx\,(1 - Ru/Ra)}{Ax} \times 100 \quad (6)$$

The table illustrates the errors which will occur when solute extraction is low and urine flow simultaneously is increased. As can be seen in this table, when the percentage of solute extraction is 90% as determined by the conventional method, correction for urine flow results in little change in the true extraction fraction. However, under conditions of both low percentage extraction and high flow rate, extraction fraction is considerably underestimated. As extraction approaches 100% and urine flow approaches zero, the original formula for extraction fraction may be employed with minimal error.

Discussion. The present report shows that under certain conditions a systematic error can be introduced into the calculation of extraction fraction. These conditions include a relatively low solute extraction and a simultaneously large removal of fluid from the kidney by non-venous routes. These are taken to be urine flow and lymphatic drainage. Previous data suggest that renal lymphatic drainage even under diuretic conditions is less than 1% of total renal plasma flow[6,7]. Therefore, we have not added this term to our equations.

Large urine volumes result from a variety of conditions, including pharmacologic diuresis[8] and osmotic diuresis[9]. Low solute extractions are generally seen with substances not secreted by the nephron, e.g., inulin and creatinine. Under certain conditions, substances secreted by the kidney which exhibit high extraction (> 80%) at low plasma concentrations exhibit low renal extraction at high plasma concentrations due to saturation of the secretory mechanism, e.g., para-aminohippurate. These

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	Calculated percentage solute extracted						
	90.0	80.0	70.0	60.0	50.0	40	30
Fraction of arterial plasma water excreted $\left(\frac{Ru}{Ra}\right)$	True extraction percentage						
0.01	90.1	80.2	70.3	60.4	50.5	40.6	30.7
0.05	90.5	81.0	71.5	62.0	52.5	43.0	33.5
0.10	91.0	82.0	73.0	64.0	55.0	46.0	37.0
0.15	91.5	83.0	74.5	66.0	57.5	49.0	40.5
0.20	92.0	84.0	76.0	68.0	60.0	52.0	44.0

Data are calculated to illustrate the error incurred in the determination of extraction fraction when urine flow is high and extraction percentage simultaneously low.

substances are also poorly extracted by the immature kidney[10,11] and in diseases of the nephron[6]. Thus, a variety of conditions exist which may be associated with errors in the calculation of extraction fraction.

As might be expected, variations in filtration fraction will affect the error in calculation of extraction fraction. Reduction of filtration fraction tends to reduce error of calculated extraction fraction because urine flow is a lower fraction of renal arterial flow.

Wolf[5] originally suggested that a correction for urine flow was necessary for calculation of renal plasma flow. His calculations show a systematic error ranging from 4 to 14% depending on urine flow. Somewhat similar errors (table) are expected for the calculation of extraction fraction, depending on urine flow and extent of solute extraction. The following calculation shows the error incurred when correction for urine flow is not made in the calculation of extraction fraction.

In the newborn dog, RPF = 1.0 ml/min/g kidney weight, GFR = 0.20 ml/min/g kidney weight, and E_x = 0.40[4]. As reported in the literature F.E. water may be 50% in certain experimental conditions in this species[9,12]. Thus, $0.20 \times 0.5 = 0.10$ ml/min/g kidney weight. Ru/Ra = 0.10/1.0 = 10%. From the table, E_x is actually 0.46 not 0.40, an error of 15%. This error will become greater as urine flow increases and solute extraction is reduced[13].

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Distribution of ^{14}C after topical application of ^{14}C-labeled 1,3-bis-(2-chloroethyl)-1-nitrosourea (BCNU) in mice

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Summary. Following topical application of ^{14}C-labeled 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU, carmustine) to the skin of mice radioactivity was found in all viscera and tissues examined. Exclusive of the gut, highest values were recorded for the liver, kidney and lung.

Topically applied 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU, carmustine) is an effective treatment for mycosis fungoides[2]. This paper reports the pattern of organ and tissue distribution of ^{14}C following the topical application of ^{14}C-labeled BCNU to mouse skin. Ethyl labeled ^{14}C-BCNU was supplied by Wm. H. Yanko, Monsanto Research Corp., at the request of Dr Vincent T. Oliverio, National Cancer Institute. The specific activity of the sample was 10.07 mCi/mmole (47.06 μCi/mg) with a radiochemical purity of 98.5%. The dorsal neck region of 7 female Swiss mice, weight 32–43 g, was shaved with an electric clippers 1 day prior to the application. 100 μl of ^{14}C-BCNU in methanol, 0.1062 mg (5 μCi), was applied to a 5 cm^2 shaved area and allowed to dry for 2 min. As a control for possible ingestion of the compound, 1 mouse was given 0.0212 mg (1 μCi) of ^{14}C-BCNU in propylene glycol s.c. and sacrificed after 6 h. The mice were placed in individual holding cages. Food and water were allowed ad libitum.

The mice were sacrificed at 1, 2, 3, 5, 6, 18 and 24 h by cervical dislocation. Carcass weights were determined, and the animals were carefully dissected. The lung, heart, liver, kidneys, spleen, brain, gut (entire gastro-intestinal tract) and pieces of muscle and fat were analyzed. After removal each tissue was immediately put in a separate, pre-weighed glass counting vial. Using a 7 ml Ten Broeck tissue homogenizer each sample was homogenized with 10–15 ml distilled water. For analysis of the ^{14}C content a published method was used[3]. This consisted of wet ashing a 2 ml sample of the homogenate with 2% potassium dichromate in concentrated sulfuric acid, and trapping the evolved $^{14}CO_2$ with ethanolamine. This was added to a scintillator fluid and counted with appropriate standards in a Beckman liquid scintillation counter. Results were expressed in μg of BCNU per g of organ (wet weight), utilizing a computer program. BCNU is rapidly degraded following i.v. or oral administration[5]. Hence the ^{14}C activity most likely represents fragments or metabolic products of the applied compound.

The table states the BCNU equivalents in mouse organs and tissues, expressed in μg/g wet weight, after a single application of 106.2 μg ^{14}C-BCNU to the shaved skin, and

Distribution of ^{14}C after application of ^{14}C-BCNU to mice[a]

	Topical application of 106.2 μg							s.c. (21.2 μg)
	1 h	2 h	3 h	5 h	6 h	18 h	24 h	6 h
Liver	3.72	2.74	2.39	1.50	0.27	0.22	0.20	0.30
Kidney	3.13	3.11	1.85	1.14	0.34	0.31	0.32	0.47
Lung	1.60	1.45	1.08	0.70	0.21	0.18	0.17	0.27
Heart	1.15	0.95	0.54	0.39	0.11	0.12	0.14	0.14
Spleen	1.08	1.43	0.94	0.70	0.03	0.19	0.19	0.05
Brain	0.53	0.37	0.36	0.31	0.11	0.11	0.10	0.13
Gut[b]	3.94	6.19[c]	4.33	1.42	0.37[c]	0.13	0.36	0.46
Feces	3.95	–	4.33	3.06	–	0.22	0.63	1.96
Muscle	0.70	0.56	0.34	0.21	0.06	0.05	0.07	0.22
Fat	0.41	0.16	0.27	0.17	0.14	0.03	0.08	0.17

[a] Expressed as μg BCNU-equivalent per g organ or tissue. [b] Entire gastro-intestinal tract. [c] Includes contents.

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