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Steven Port
Sinai Samaritan Medical Center
Milwaukee, Wisconsin

Ken Nichols
St. Lukes-Roosevelt Hospital Center
New York, New York

Dosimetric Models and S Factors for Radiation Doses to the Bladder Wall in Children Receiving Therapeutic Iodine-131-MIBG

TO THE EDITOR: With the introduction of [^{131}I]metaiodobenzylguanidine (MIBG) therapy for the treatment of neuroblastoma, there is a need for accurate estimation of radiation dose to the urinary bladder in children. Bladder dosimetry is of particular importance when MIBG therapy is part of a combined modality treatment, either in combination with total body external beam irradiation (1) or chemotherapy agents (2) where additive damage to the bladder could become clinically significant. Published information on bladder doses from [^{131}I]MIBG is relatively scarce (3), but there are at least two publications which focus on bladder dosimetry in children (4,5), each using a different calculation method. We evaluated these publications in view of our initial experience with the new MIRD urodynamic model since the original publications had errors (6,7). The exercise raises doubts about the certainty of S factors previously used in children.

In the United Kingdom Children's Cancer Study Group (UKCCSG) publication (4), data on urinary output of radionuclides were collected by measuring whole-body radioactivity before and after voiding in five noncatheterized patients who had received therapeutic [^{131}I]MIBG. All five patients had been hydrated (3 liter/m^2 for at least 24 hr) and had voided frequently (every 1-5 hr). No patients exceeded 10.4 yr of age. Cumulative activity in the bladder was taken to be the sum of the products of the activity in each void and the mean residence time, the latter being one-half the time between voids.

Dose to the bladder wall was then determined from the product of cumulated activity and the appropriate S factor (dose per unit cumulated activity from bladder contents to surface of bladder

wall) at each age; the S factor was obtained from Report 73 of the National Council on Radiation Protection and Measurements (8). The estimated radiation doses to the bladder wall per unit administered activity of ^{131}I ranged from 2.2–5.3 mGy/MBq.

The approach used by a Task Group of the International Commission on Radiological Protection (ICRP) (5) was different in that cumulated activity in the bladder was derived from a mathematical model in which the rate of renal excretion of MIBG is determined from the whole-body retention curve, which is described by a series of exponential functions. The interval between voids is taken to be constant (3.5 hr) and the same for all ages. A fixed average bladder content is used, i.e., the model does not allow for bladder filling, but allowance is made for variation of bladder contents with age: 200 ml for adults and 152, 97, 61 and 31 ml for 15-, 10-, 5- and 1-yr-old children, respectively. The Task Group derived S factors for final dose calculations and estimated doses to the bladder wall ranged from 0.73 mGy/MBq at age 15 yr to 3.3 mGy/MBq at age 1 yr.

Although the UKCCSG patients were hydrated, there appeared to be reasonable correspondence between these two sets of dose estimates, considering the differences in methodology. We have been investigating the application of the new MIRD urodynamic model (corrected version) (6,7) in children. This model allows for bladder expansion, permits choice of urine flow, void time and initial bladder contents. Our work has brought to light substantial discrepancies between the S factors employed by the NCRP (8) and ICRP (5). Although the factors in the latter report are not explicitly calculated, it is possible for them to be determined through back calculation by dividing the estimated dose per unit activity (mGy/MBq) by the cumulated activity in the bladder (MBq-hr), an expression for which is given in the report. The calculation requires whole-body clearance to be expressed as a sum of exponential components. Two components of whole-body clearance of MIBG are identified in the ICRP report and apply to all age groups, namely, 36% with a biological half-period of 3 hr and 63% with a biological half-period of 33.6 hr. All MIBG excretion is taken to occur by the renal route. Our mean retention curve in seven children was similar. The two components were 57.5% with a half-period of 9 hr and 42.5% with a half-period of 51.1 hr.

ICRP S factors derived in this way for different ages are compared with those tabulated in the NCRP report (8) (Table 1). Our own S factors for the nonpenetrating component of ^{131}I radiation calculated by standard methods (9) and using the ICRP values for average bladder contents at different ages are also included. These comparisons show the NCRP S factors to be greater than the others. In the NCRP report, no information is given for bladder content volume at different ages, but they would need to be much

TABLE 1
Comparison of S Factors

Age (yr)	mGy/MBq-hr		
	ICRP	NCRP	Bolster et al.*
Newborn	—	21.05	—
1	1.94	4.81	1.80
5	1.00	3.22	0.92
10	0.65	—	0.58
15	0.43	—	0.37
Adult†	0.35	—	0.28

*Nonpenetrating component only.
†S values for adults in this table are similar to the values in *MIRD Pamphlet No. 10.*

TABLE 2
Bladder Wall Dose (mGy/MBq) at Different Ages

Age (yr)	ICRP model	New MIRD model	Daytime urine flow (ml/min)
1	3.30	2.33	0.44*
5	1.70	1.99	0.52
10	1.10	1.33	0.79
15	0.73	1.21	0.87
Adult	0.59	0.96	1.11

*At half this value, the estimated dose is approximately doubled; at twice this value, the dose is halved.

lower (by up to a factor of 3 at age 1–5 yr) than the ICRP values to produce the relatively high S factors. Whether low values are physiologically realistic is doubtful.

Further evidence in favor of the ICRP values is provided in Table 2, where the estimated bladder wall doses for different ages in the ICRP report are compared with our own exploratory estimates using the new MIRD bladder model (6,7). As in the ICRP report, the voiding interval was set at 3.5 hr for all ages, the first void taking place 3.5 hr after administration of [131I]MIBG. Urine outputs at each age interval are those for a normal state of hydration and were obtained from standard tables (10). Although the new model is more realistic physiologically than the ICRP bladder model, its application in adults has shown that simpler models can provide reasonable dose estimates (within a factor of two) (6,7) for a variety of radiopharmaceuticals. The fact that the two dose estimates in Table 2, albeit for a variety of ages, are not markedly different would lend support for the ICRP S factors, in preference to those published by the NCRP. Our exploratory work in the new bladder model demonstrates the importance of adequate hydration and resultant urine flow in reducing radiation dose to the bladder wall, a feature that may be of increasing importance if dose escalation of [131I]MIBG occurs, particularly in conjunction with chemotherapy or external beam irradiation.

ACKNOWLEDGMENT

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A.A. Bolster
T.E. Hilditch
T.E. Wheldon
Western Infirmary
Cancer Research Campaign Beatson Laboratories
Glasgow, United Kingdom

Use of Bleomycin in Radiochemotherapy

TO THE EDITOR: We would like to congratulate Even-Sapir et al. (1) for their article in which they demonstrated that the uptake of 57Co-bleomycin predicts the outcome of patients with lung cancer. They showed that lung tumors with a high uptake of 57Co-bleomycin late after injection responded poorly to chemotherapy and were associated with shorter survival than tumors showing lower uptake. DNA-bound bleomycin may correlate with the absolute activity detected by SPECT, and this agrees with the nature of the drug having major effects during the G2-phase (2). It is widely known that bleomycin has targeting abilities in lung cancer (3). Bleomycin can be used as a chemotherapeutic agent and complexes of radioactive bleomycin are also conceivable for therapy. In fact, we have studied a low-pH 111In-bleomycin complex (BLMC) in head and neck cancers. We have found good sensitivity (93%) and specificity (100%) in the diagnostic staging of 13 head and neck cancer patients (4). The half-life of 111In is approximately 2 hr in serum and urine. The tumor-to-serum ratio was highest at 3.6/1. We think that this BLMC has many advantages compared to other bleomycin compounds and is suitable for therapeutic use. It is obvious that the patients with a poor outcome presented by Even-Sapir et al. should be the first to receive BLMC.

The facts above demonstrate the importance of the observation by Even-Sapir et al. (1) and demonstrate an additional way to characterize lung cancer in vivo. Furthermore, Even-Sapir et al. introduced a method to select patients that would benefit from bleomycin therapy. Indium-111-BLMC has some additional advantages over 57Co-labeled bleomycin: accumulation in bone marrow is limited and BMLC has a more convenient half-life. They have similar uptake in lung and kidney. Nevertheless, pulmonary toxicity, may be the limiting factor, although in patients with lung cancer it may provide an undeniable benefit.

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Kalevi Kairemo
Antti Jekunen
Hans Ramsay
Hilkka Jääskelä-Saari
Helsinki University Central Hospital
Helsinski, Finland

REPLY: We thank Kairemo and his colleagues for their kind words concerning our study. One should realize, however, that we did not use bleomycin labeled with 57Co (Co-bleo) as an agent for diagnosing lung tumors. We also did not use it in the current study as a labeled chemotherapeutic agent for quantitation of targeting. Co-Bleo was used as an agent similar to thymidine or deoxyuridine to determine cell kinetics in vivo (1). The results of our study indicate that Co-Bleo uptake is related to response to