A COMPARISON OF MECKEL'S SCINTIGRAPHY IN CHILDREN: PREMEDICATION WITH PENTAGASTRIN VERSUS PENTAGASTRIN PLUS H_2-RECEPTOR BLOCKER (RANITIDINE)

Supatporn TEPMONGKOL, M.D., Sydney HEYMAN, M.D.

ABSTRACT

BACKGROUND: Premedicating with various drugs prior to Tc-99m pertechnetate scintigraphy has been proposed for augmenting the detection of Meckel's diverticulum. This study aims to document the actual sensitivity, specificity, accuracy, positive, and negative predictive values of premedication with pentagastrin and pentagastrin plus ranitidine, which has not been documented before, and to compare the efficacy of these two protocols.

METHODS: Two premedication protocols were followed. 181 Meckel's scans with pentagastrin stimulation were performed in 180 patients, and 49 scans with both pentagastrin and ranitidine stimulation in 49 patients. These were retrospectively reviewed and analysed for the efficacy of each protocol, and the two groups were compared.

RESULTS: The sensitivity, specificity, accuracy, positive, and negative predictive values of the group premedicated with pentagastrin were 71.4%, 99.4%, 96.1%, 93.8%, 96.4%, respectively, and the group with pentagastrin plus ranitidine were 80%, 100%, 98%, 100%, 97.8%, respectively. Considering those patients in whom there was an identifiable cause for the symptoms, including Meckel's diverticulum the sensitivity, specificity, accuracy, positive, and negative predictive values were 71.4%, 99.1%, 94.8%, 93.8%, 95.0%, respectively, for the pentagastrin group, and 80%, 100%, 97.4%, 100%, 97.1%, respectively for the pentagastrin plus ranitidine group. There was no significant statistical difference in the sensitivity and specificity between these two groups ($p>0.05$). Conclusion: Meckel's scans using pentagastrin plus ranitidine slightly, but not significantly improves sensitivity and specificity for the detection of Meckel's diverticulum compare with pentagastrin alone. Positive and negative predictive values of both premedication protocols are very high, ranging from 93.8%-100%.

Key Words : Meckel's; ectopic gastric mucosa; pentagastrin; H2 receptor blocker; Tc-99m pertechnetate

Nuclear Medicine Division, Department of Radiology, Chulalongkorn Hospital, Bangkok, Thailand.
Nuclear Medicine Division, Department of Radiology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA.
The work was performed at : Nuclear Medicine Division, Department of Radiology, Children's Hospital of Philadelphia

For correspondence and reprints request, contact: Supatporn Tepmongkol, M.D. Nuclear Medicine division, Department of Radiology, Chulalongkorn Hospital, Rama IV road, Bangkok, Thailand., Tel (662) 2564283-4, Fax (662) 2564162, Email : supatporn@hotmail.com

Abbreviated Title: A comparison of Meckel's scan with pentagastrin vs pentagastrin plus ranitidine.
A Comparison of Meckel's Scintigraphy in Children: Premedication with Pentagastrin versus Pentagastrin plus H_2-receptor Blocker (Ranitidine)

INTRODUCTION

Tc-99m pertechnetate is known to concentrate in gastric mucosa[1,2,3] and was proposed for use in the non-invasive diagnosis of Meckel's diverticulum with ectopic gastric mucosa by Harden et al in 1967.[3] In 1970, the method was introduced into clinical practice by Duszynski et al.[4,5,6] This conventional method has become an established routine procedure in children and adults for almost 30 years. The sensitivity is reportedly in the range of 75-85% . The specificity was found to be 79-95%.[6,7,8]

Although the utility of Meckel's scanning is well documented, false negative rates as high as 50% have been reported.[9,10] Using modern equipment and more careful attention to the technique, the false negative rate was reduced to 15-20%.[8,11,12,13] To overcome the false negative problems several pharmacological interventions have been proposed including premedicating with pentagastrin[14,15,16,17,18] or cimetidine[19,20] shown to be of value in animal experimental studies. Unfortunately, only isolated case reports have been published on the efficacy of pentagastrin,[21,22] cimetidine[23,24,25] and the combination of pentagastrin plus ranitidine in humans.[26] This study is aimed to retrospectively evaluate the efficacy of the Meckel's scan using premedication with pentagastrin or pentagastrin plus an H2-receptor blocker which has not been previously reported. Furthermore, it was done to compare the sensitivity and specificity of these 2 premedication protocols.

MATERIALS AND METHODS

PATIENT POPULATION

From August 1980 to June 1998, there were 231 patients referred to the Nuclear Medicine division at the Children's Hospital of Philadelphia for the diagnosis of Meckel's diverticulum. There were 138 males and 93 females, aged 1 month to 24 years, with mean age of 5.63± 5.2 years. The patients presented with a history of hematochezia, either painless or painful, melena, abdominal pain alone, or only heme positive stools.

The patient population was divided into 2 groups. One group received pentagastrin stimulation alone and included patients from August 1980 to November 1991. The rest of the patients were studied with pentagastrin plus ranitidine stimulation.

SCINTIGRAPHY

The Meckel's scan was performed using Tc-99m pertechnetate in a dose of 555 MBq/1.73 m^2 (15mCi/1.73 m^2) , minimum 70 MBq (2 mCi). The patients fasted approximately 4 hours prior to the study.

Before starting the study, those in group 2 received 1 mg/kg of ranitidine hydrochloride (Zantac-H2 receptor blocker) intravenously over 10 minutes, 30 minutes prior to injecting the radiopharmaceutical. A subcutaneous injection of pentagastrin (6μg/kg) was given 20 minutes before injecting the radiopharmaceutical. Those in group 1 were premedicated with pentagastrin only. Studies were performed using either a Siemens orbiter or Sophy DS7 gamma camera with LEAP collimator. The injection of pertechnetate was given as a bolus. The earlier studies were acquired in analogue mode as 2 second/frame for 1 minute and then at 5 minute intervals for 30 minutes, followed by anterior, right lateral and posterior views. Later studies were acquired in digital mode. The initial flow was recorded at 1 sec/frame for 60 seconds. Thereafter dynamic images were recorded at 30 second/frame for 60 frames in 128x128 word mode, and reframed into 1 min/frame for hardcopy images. Anterior, posterior,

and right lateral images were obtained after the dynamic phase for 500 Kcounts in 256x256 word mode. The bladder was emptied if necessary and a repeat anterior and right lateral view obtained. Potassium perchlorate (6 mg/kg) was given orally at the completion of the study.

STATISTICS

Sensitivity, specificity, accuracy, positive predictive value, and negative predictive value were used for evaluating the efficacy of both tests. Critical ratio is used for comparing the sensitivity and specificity of the two premedication protocols.

RESULTS

181 Meckel's scans with pentagastrin stimulation were performed in 180 patients, and 49 scans with both pentagastrin and ranitidine stimulation in 49 patients. Of 180 patients, 2 patients were studied twice, one patient with pentagastrin stimulation in both studies and 1 patient with pentagastrin stimulation in the first study and pentagastrin plus ranitidine the second time. There are 2 patients that were excluded from the study; one because of inadequate workup to identifiy the bleeding cause, and the other because of a suboptimal Meckel's scan.

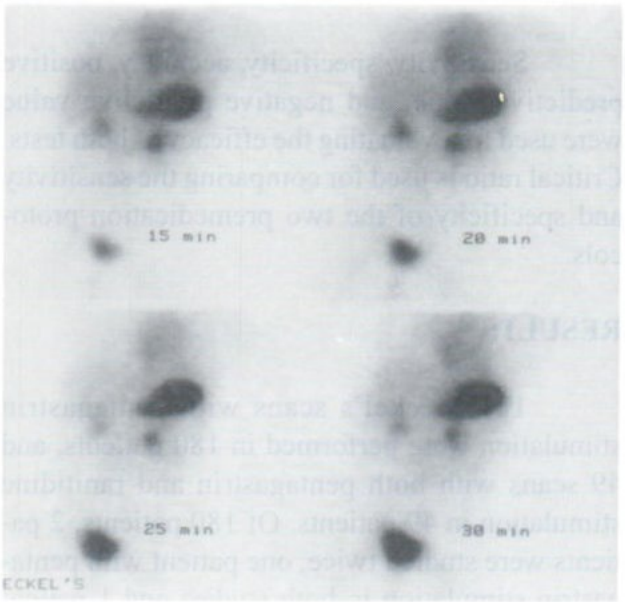
All the cases with positive scans were confirmed by surgery giving a true positive for Meckel's diverticulum in 15/181 scans using pentagastrin (Fig. 1) and 4/49 scans with pentagastrin plus ranitidine (Fig. 2). The sensitivity, specificity, accuracy, positive, and negative predictive values are shown in Table 1. Of those with true negative scans, in whom a cause for the symptoms could be identified, there were 113/159 receiving pentagastrin only and 33/44 pentagastrin plus ranitidine. These etiologies were proven by either endoscopy, biopsy, radiologic contrast examination, stool exam, or stool culture (Table 2). One of these was shown to be rectal duplication with mildly inflammed ectopic gastric mucosa. Of the other, 46/159 true negative patients with pentagastrin and 11/44 true negative patients with pentagastrin plus ranitidine were assumed not to have Meckel's diverticulum because of extensive negative workups and absence of further bleeding on follow up examination. There was 1 patient with pentagastrin stimulation who had a false positive result because of very early excretion of Tc-99m pertechnetate from the stomach into left upper quadrant of abdomen causing misinterpretation. There were no false positive studies with pentagastrin plus ranitidine. There were 6 false negative scans with pentagastrin. In one of these, the resected Meckel's diverticulum did not have gastric mucosa but had pancreatic tissue. For two of the false negative results, the pathological reports were not available. Another false negative scan showed early excretion of radiotracer from the stomach into small bowel with much activity on the left side of abdomen at 20 minutes. At 25 minutes there was a small focus on the right side of abdomen which was thought to be progression of small bowel activity. A fifth scan was completely negative but the pathological report revealed a Meckel's diverticulum with gastric heterotopia and ulcer. There was one patient with a false negative scan in whom the study was repeated. He received pentagastrin the first time with a false negative result. Following premedication with pentagastrin and ranitidine on the second occasion, the scan was strongly true positive for Meckel's diverticulum. There was one false negative study with pentagastrin plus rantidine (Fig. 3) in which early images showed a small focus overlying the bladder, which could not subsequently be separated from it. The pathological report showed a Meckel's diverticulum with a large area of pancreatic tissue, but also containing gastric mucosa.

If those cases in whom documented conditions other than Meckel's were found to explain the patients symptoms are considered as true nega-

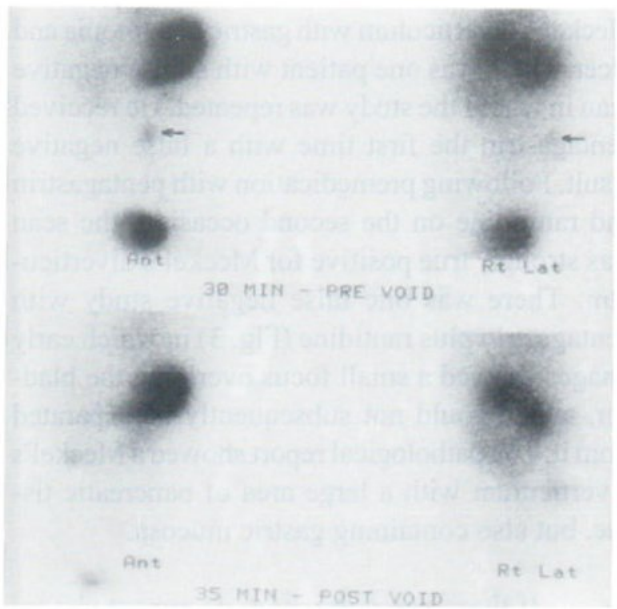
tive results, the sensitivity, specificity, accuracy, positive, and negative predictive value are shown in Table 3. One patient in this group, was scanned twice with pentagastrin stimulation and both studies were negative for Meckel's diverticulum. This patient had multiple gastrointestinal vascular malformations causing the bleeding.

When comparing the sensitivity and specificity between the study with pentagastrin and the study with pentagastrin and ranitidine, there are no significant differences ($p>0.05$) using critical ratio as shown in Table 4.

1A

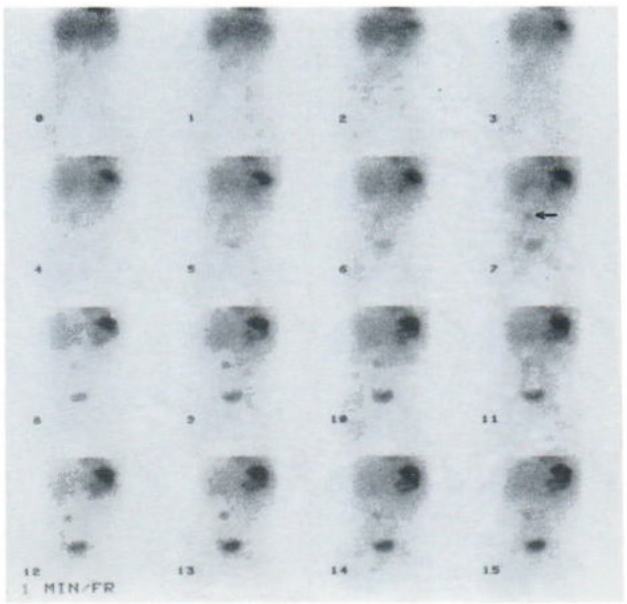


1B

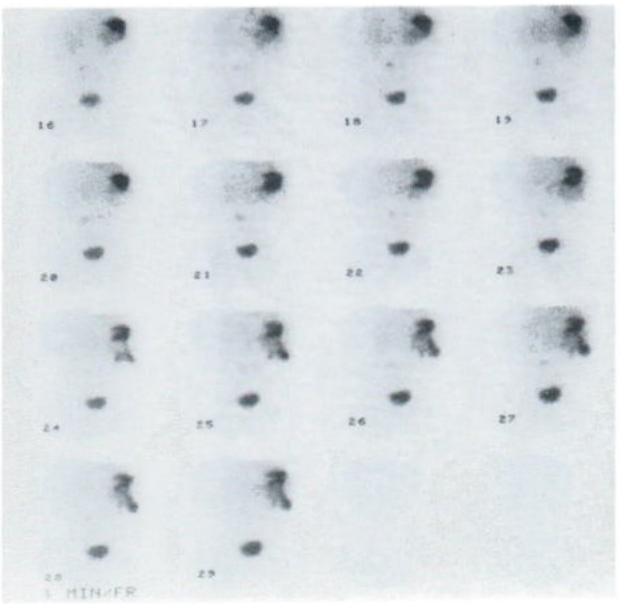


1C

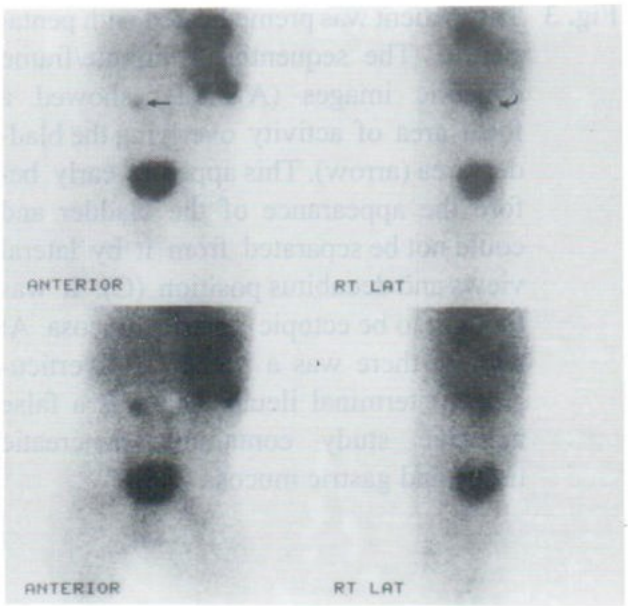
Fig. 1 This patient was premedicated with pentagastrin. The early images (A and B) showed activity at left side of abdomen (arrow) which was at first thought to be excretion of Tc-99m pertechnetate into the left kidney. The lateral view was not done until 30 minutes. At 30 minutes (C), the activity overlying left kidney moves anteriorly in the midline of abdomen (arrows) and moves to the right side after voiding. This was a true positive for Meckel's diverticulum.



2A

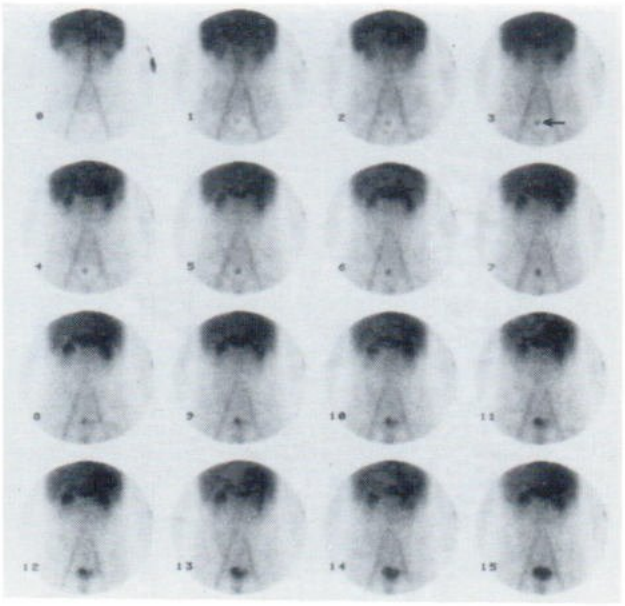


2B

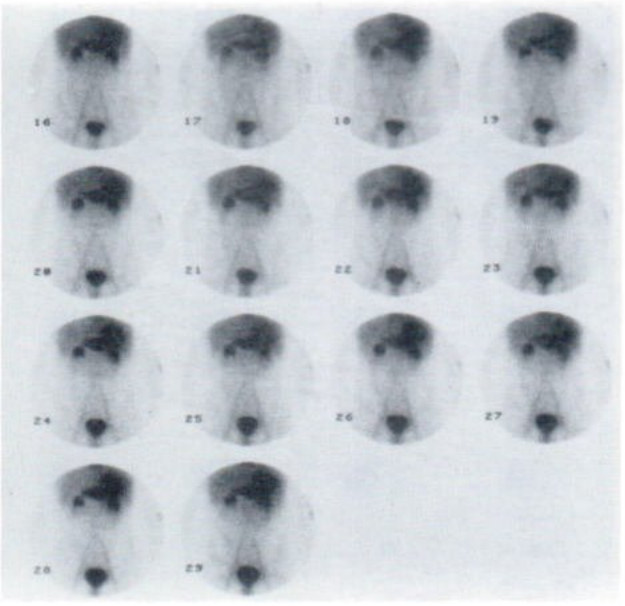


2C

Fig. 2 After premedication with pentagastrin and ranitidine, the sequential 1 minute/frame images (A and B) showed focal accumulation of Tc-99m pertechnetate at right mid abdomen (straight arrow). The uptake in creased parallel to that of the stomach. On the static images (C), the abnormal uptake area was on the right side on anterior view (straight arrow) and midway between anterior and posterior abdominal walls on lateral view (curve arrow). The pathological result showed Meckel's diverticulum with ectopic gastric mucosa. This was a true positive study.



3A



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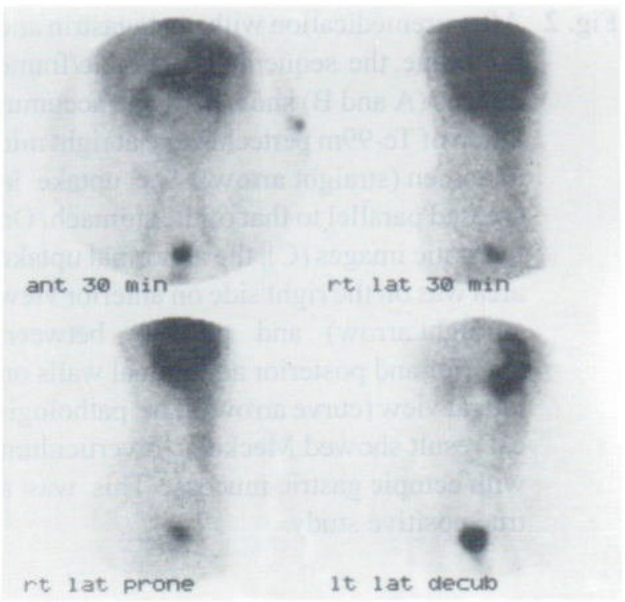

3C

Fig. 3 This patient was premedicated with pentagastrin. The sequential 1 minute/frame dynamic images (A and B) showed a focal area of activity overlying the bladder area (arrow). This appeared early before the appearance of the bladder and could not be separated from it by lateral views and decubitus position (C). It was thought to be ectopic gastric mucosa. At surgery, there was a Meckel's diverticulum. At terminal ileum. This was a false negative study containing pancreatic tissue and gastric mucosa.

Table 1. Efficacy of Tc-99m pertechnetate Scan to Detect Meckel's Diverticulum

Premedication	Patients				Percent				
	TP	TN	FP	FN	Sens.	Spec.	Acc.	PPV	NPV
Pentagastrin (N=181)	15	159	1	6	71.4	99.4	96.1	93.8	96.4
Pentagastrin+ Ranitidine (N=49)	4	44	0	1	80.0	100	98.0	100	97.8

TP = true positive, TN=true negative, FP=false positive, FN=false negative, Sens.=sensitivity, Spec.=specificity, Acc.=accuracy, PPV=positive predictive value, NPV=negative predictive value

Table 2. Diseases Causing GI Symptoms In True Negative Studies

Disease	Studies	
	pentagastrin (N=113)	pentagastrin+ranitidine (N=33)
Upper GI inflammation /ulcer	22	5
Lower GI inflammation /ulcer	42	15
Intestinal polyp	14	3
Lymphoid hyperplasia	15	5
Vascular malformation	11	0
Bowel ischemia	2	1
Clotting defect	1	1
Functional abdominal pain	2	0
Miscellaneous	4	3

Table 3. Efficacy of Tc-99m pertechnetate Scan to Detect Meckel's Diverticulum (in patients proven to have positive disease causing symptoms)

Premedication	Patients				Percent				
	TP	TN	FP	FN	Sens.	Spec.	Acc.	PPV	NPV
Pentagastrin (N=135)	15	113	1	6	71.4	99.1	94.8	93.8	95.0
Pentagastrin+ Ranitidine (N=38)	4	33	0	1	80.0	100	97.4	100	97.1

TP = true positive, TN=true negative, FP=false positive, FN=false negative, Sens.=sensitivity, Spec.=specificity, PPV=positive predictive value, NPV=negative predictive value

Table 4. Comparison between sensitivity, specificity, accuracy, positive, and negative predictive value of the study with pentagastrin and pentagastrin plus ranitidine.

	CRITICAL RATIO	
	All patients	+ve disease patients
Sensitivity	0.44 (NS)	0.44 (NS)
Specificity	1.27 (NS)	1.08 (NS)

NS = non significant ($p > 0.05$)

DISCUSSION

Pentagastrin[22] and cimetidine[23,24,25] have been used to improve the rate of detection of ectopic gastric mucosa by Tc-99m pertechnetate scan. Pentagastrin is a synthetic polypeptide that contains the active N-terminal 5-amino acid residue of gastrin, a natural hormone produced from the gastric antrum. Like gastrin, pentagastrin stimulates gastric mucosal blood flow and stimulates gastric acid secretion by acting on parietal cells. Pepsin and intrinsic factor are increased as well.[14,15] An experimental study in mice done by Khettery et al[15] showed that pentagastrin increased the fractional uptake of Tc-99m pertechnetate from 25% of injected dose to 65% at 30 minutes. Anderson et al[18] also showed that pentagastrin produced accelerated uptake and also achieved higher uptake levels of the radionuclide in both the stomach and ectopic gastric mucosa, but resulted in early visualization of the duodenum and a washout effect on the radioisotope within the Meckel's diverticulum. In our study very early visualization of the small bowel was seen in two cases with pentagastrin stimulation alone which caused misinterpretation, one as a false positive for Meckel's diverticulum and the other as a false negative because the activity obscured the true ectopic gastric mucosa. Secretion from the ectopic gastric mucosa into the ileum, along with the potent stimulatory effect on GI motility via a direct effect on smooth muscle, and dilution in an increased volume of gastric and intestinal juices produced by pentagastrin, decreases the peak pertechnetate activity that could be achieved in the Meckel's diverticulum. This may be one of the reasons for the false negative results in our study with pentagastrin alone.

Ranitidine is an H2-receptor blocker, like cimetidine which decreases gastric basal hydrochloric output by 50%.[19] Sagar and Piccone[19] showed that pretreatment with cimetidine increases pertechnetate uptake 4.4 times in the gastric wall of dogs and concluded that cimetidine had no effect on concentration of pertechnetate into gastric mucosa, but, similar to its effect on hydrochloric acid, blocks secretion of technetium into the gastric lumen. It inhibits acid secretion stimulated by gastrin and also decreases blood flow.[21] Cimetidine is reported to inhibit the stimulatory effect of pentagastrin on pertechnetate uptake so that it is suggested that these two drugs not be used combination;[21,27,28] however, some paper[27,29] discovered that this effect may not be as potent as initially reported. Heyman[26] reported a case of Meckel's diverticulum which was negative on the first study with pentagastrin stimulation alone and was obviously positive on the second scan with pentagastrin while the patient was on oral ranitidine. This is one of our study cases. The question is raised whether a false negative with pentagastrin may be corrected by adding ranitidine using the principle that pentagastrin enhances the uptake of pertechnetate into cell, while ranitidine promotes its retention. After the finding in this case, ranitidine was used in combination with pentagastrin in subsequent scans. In our study, when comparing the sensitivity and specificity between the two groups, it seems that the group with pentagastrin plus ranitidine is better, but there was no statistically significant difference. Although not proven to be significantly better, we are now know that using ranitidine concurrently with pentagastrin does not lower the detection rate of ectopic gastric mucosa. In contrast, it slightly improves the detection of it. This may imply that in humans the additive effect of these two drugs are stronger than the inhibitory effect. Thus, we suggest that patients who undergo Meckel's scintigraphy with pentagastrin stimulation, and who are currently on an H2-receptor blocker, need not have the medication withdrawn before having the scan.

There was only one false positive scan in

the pentagastrin group as discussed. This shows that there is only a minimal chance of incorrectly sending a patient to surgery when using this agent and even less so when using ranitidine in combination. There are many reasons why the scan may miss the lesion (false negative study).[30,7,11] In our patients there were a total of 7 false negatives. One showed early excretion of activity into small bowel obscuring the true lesion. In the second case, there was no gastric mucosa but pancreatic tissue was seen. The third showed focal activity overlying and inseparable from the bladder with mainly pancreatic tissue and less gastric mucosa histologically. One patient was scanned twice. The first scan was negative with pentagastrin alone, but becoming positive when repeated while on oral ranitidine. In two of the seven cases pathological reports were not available so that the presence of gastric mucosa could not be confirmed. In one, non-visualization of the lesion could not be explained. Reported explanations for false negatives including absent or insufficient gastric mucosa or lack of mucoid surface cells, was thought to concentrate pertechnetate,[31,32] or there may be an effect of pentagastrin causing a "washaway" of activity from the Meckel's as mentioned above, or the lesion may be located near some organ, such as the bladder, which normally accumulates radioactivity and effectively obscures it.

CONCLUSION

In conclusion, we have shown that combining an H2-blocker (ranitidine) with pentagastrin for premedication in children undergoing Meckel's scintigraphy does not lower the detection rate when compared with pentagastrin alone. On the contrary, both the sensitivity and the specificity are slightly improved, though the differences are not statistically significant. The positive and negative predictive values of both premedication protocols are very high in the range of 93.8% to 100%. Thus, we suggest that when Meckel's scintigraphy is performed using pentagastrin for premedication, it is not necessary to discontinue an H2-blocker in those patients who have been previously placed on this medication.

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REFERENCES

1. McAfee JG, Fueger CF, Stern HS, et al. ^{99m}Tc pertechnetate for brain scanning. J Nucl Med 1964;5:811-827
2. Hoffmeyr NG. Stomach scanning after intravenous ^{99m}Tc administration. A preliminary report. S Afr Med J 1967;41:572-575
3. Harden RMcG, Alexander WD, Kennedy I. Isotope uptake and scanning of stomach in man with ^{99m}Tc pertechnetate. Lancet 1967;1:1305-1307
4. Duszynski DO, Jewett TC, Allen JE. Potentiallities of abdominal scanning with ^{99m}Tc-sodium pertechnetate [Abstarct]. J Nucl Med 1970;11:628
5. Duszynski DO, Anthone R. Jejunal intussusception demonstrated by ^{99m}Tc pertechnetate and abdominal scanning. Am J Roentgenol 1970;109:729-732
6. Jewett TC, Jr, Duszynski DO, Allen JE. The visualization of Meckel's diverticulum with ^{99m}Tc pertechnetate. Surgery 1970;68:567-570
7. Convay JJ and the Pediatric Nuclear Club of the Society of Nuclear Medicine. The sensitivity, specificity and accuracy of radionuclide imaging of Meckel's diverticulum [Abstract]. J Nucl Med 1976;17:553

8. Sfakianakis GN, Convay JJ. Detection of ectopic gastric mucosa in Meckel's diverticulum and in other aberrations by scinitigraphy. I. pathophysiology and 10-year clinical experience. J Nucl Med 1981; 22:647-654
9. Singh PR, Russell CD, Dubovski EV, et al. Technique for scanning for Meckel's diverticulum. Clin Nucl Med 1978;3:188-192
10. Wilton G, Froelich JW. The "false-negative" Meckel's scan. Clin Nucl Med 1982; 7:441-443
11. Sfakianakis GN, Convay JJ. Detection of ectopic gastric mucosa in Meckel's diverticulum and in other aberrations by scintigraphy. II. Indications and methods-A 10-year experience. J Nucl Med 1981;22:732-738
12. Sfakianakis GN, Haase GM. Abdominal scintigraphy for ectopic gastric mucosa: A retrospective analysis of 143 studies. AJR 1982;138:7-12
13. Convay JJ. Radionuclide diagnosis of Meckel's diverticulum. Gastrointest Radiol 1980;5:209-213
14. Swanson DP, Syrja MJ, Anderson SJ, et al. Formulary: Pharmacologic interventions in nuclear medicine. In: Thrall JH, Swanson DP, eds. Diagnostic Interventions in Nuclear Medicine. Chicago: Year Book Medical. 1985:247-267
15. Khettery J, Effmann E, Grand RJ, et al. Effect of pentagastrin, histalogue, glucagon, secretin, and perchlorate on the gastric handling of Tc-99m pertechnetate in mice. Radiology 1976;120:629-631
16. Holder LE, Ashare AB, Smith W, et al. Pentagastrin: A new drug for stimulating gastric secretion of pertechnetate [Abstract]. J Nucl Med 1975;16:535-535
17. Sfakianakis GN, Anderson GF, King DR, et al. The effect of gastrointestinal hormones on the pertechnetate imaging of ectopic gastric mucosa in experimental Meckel's diverticulum. J Nucl Med 1981; 22:678-683
18. Anderson GF, Sfakianakis GN, King DR, et al. Hormonal enhancement of Tc-99m pertechnetate uptake in experimental Meckel's diverticulum. J Ped Surg 1980; 15:900-905
19. Sagar VV, Piccone JM. The effect of cimetidine on blood clearance, gastric uptake, and secretion of Tc-99m pertechnetate in dogs. Radiology 1981;139:729-731
20. Yeker D, Buyukunal C,Benli M, et al. Radionuclide imaging of Meckel's diverticulum: cimetidine versus pentagastrin plus glucagon. Eur J Nucl Med 1984;9:316-319
21. Keane FB, O'Connor M, Stephens RB, et al. An assessment of dynamic gastric scanning with Tc-99m pertechnetate. Br J Surg 1982;69:383-385
22. Treves S, Grand RJ, Eraklis AJ. Pentagastrin stimulation of Tc-99m uptake by ectopic gastric mucosa in a Meckel's diverticulum. Radiology 1978;128:711-712
23. Petrokubi RJ, Baum S, Rohrer GV. Cimetidine administration resulting in improved pertechnetate imaging of Meckel's diverticulum. Clin Nucl Med 1978;3:385-388
24. Diamond RH, Rothstein RD, Alavi A. The role of cimetidine-enhanced technetium-99m pertechnetate imaging for visualizing Meckel's diverticulum (clinical conference). J Nucl Med 1991;32:1422-1424
25. Baum S. Pertechnetate imaging following cimetidine administration in Meckel's diverticulum of the ileum. Am J Gastroenterol 1981;76:464-465

26. Heyman S. Meckel's diverticulum: possible detection by combining pentagastrin with histamine H2 receptor blocker. J Nucl Med 1994;35:1656-1658
27. Shapiro B, Gross MD. Interventional studies of the upper gastrointestinal tract. In: Thrall JH, Swanson DP, eds. Diagnostic Interventions in Nuclear Medicine. Chicago: Year Book Medical. 1985:204-225
28. Datz FL, Christian PE, Hutson WR, et al. Physiological and pharmacological interventions in radionuclide imaging of the tubular gastrointestinal tract. Sem Nucl Med 1991;21:140-152
29. Aadland E, Berstad A, Semb LS. Inhibition of pentagastrin-stimulated gastric secretion by cimetidine in healthy subjects. In: Burland WL, Simkins MA, eds. Cimetidine. Oxford: Excerpta. 1977:87-97
30. Canty T, Meguid MM, Eraklis AJ. Perforation of Meckel's diverticumlum in infancy. J Pediatr Surg 1975;10:189-193
31. Chaudhuri T.K., Polak JJ. Autoradiographic studies of distribution in the stomach of Tc-99m pertechnetate. J Nucl Med 1976;17:559(A)
32. Marsden DS, Alexander C, Yeun P, et al. Autoradiographic explanation for the uses of Tc-99m in gastric scintiphotography. J Nucl Med 1973;14:632A