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would measure expectations before pharmacies launched their Web sites. It is possible that experience with this technology might have caused respondents to erroneously recall expectations that would be closer to what was actually experienced. In such a situation, discrepancies between contributions achieved and reported expectations may likely be moderated and lead to more conservative estimates of differences.

The study had a low response rate of 20.2%. However, the nonresponse bias survey results showed that the prevalence of Internet presence, plans for Internet presence, and most of the demographic variables did not differ significantly between respondents and nonrespondents. Comparison of responses from early and late respondents also showed no significant differences in the prevalence of Internet presence and demographic variables. These results provide some measure of evidence that the findings of this study are generalizable to the intended population. However, the limitations should be noted in interpreting our findings.

Conclusion

Although independent pharmacy owners did not indicate high expectations for their Web page in terms of attracting new customers, increasing sales, or enhancing customer service, the actual contribution of their Web pages to all of these business functions were below expectations. Higher expectations for pharmacy Web pages appeared to be associated with more comprehensive services being offered online and, in turn, to greater actual contributions of the Web page to business functions. For independent community pharmacies, the greatest potential of Web pages may lie in enhancing services or reducing their cost.

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Reliability of Saliva Hormone Tests

Jolena Hagen, Nicolette Gott, and Donald R. Miller

Recent reports concerning the safety of hormone replacement therapy (HRT) have led many women to seek alternative ways to treat menopausal symptoms. A new alternative that has become very popular is bioidentical HRT.[1] This therapy is often based on the results of saliva hormone tests, which may be purchased from pharmacies and physician offices or over the Internet. Compounding pharmacies individualize HRT based on the results of these tests.

Although saliva hormone testing is easy and convenient for a patient to perform at home, it has potential problems.[2–4] Given the importance of these tests to compounding pharmacists, we decided to perform a simple check on the tests' reliability.

Objective

Our objective was to examine the reliability of two commonly used laboratories in assaying identical sets of saliva samples.

Methods

We purchased saliva hormone kits made by two different labora-

Table 1. Saliva Hormone Test Results

Patient Description	Lab A Estradiol (pg/mL)	Lab B Estradiol (pg/mL)	Lab A Progesterone (pg/mL)	Lab B Progesterone (pg/mL)	Lab A Testosterone (pg/mL)	Lab B Testosterone (pg/mL)
1: 23-yo woman on contraceptives	2.5	0.6	58	119	28	28
1: 40-yo woman	1.5	0.8	114	147	14	25
1: 50-yo woman on HRT	3.2	< 0.3	181	168	24	23
2: 23-yo woman on contraceptives	1.8	1.8	27	194	26	17
2: 40-yo woman	1.4	0.8	31	175	22	16
2: 50-yo woman on HRT	5.1	0.7	159	204	32	13
3: 48-yo perimenopausal woman	2.7	1.3	27	157	131	63

HRT = hormone replacement therapy; pg/mL = picograms/milliliter, yo = years old.

tories. Three participants provided saliva samples to each laboratory. Two of the participants were 23-year-old women, and the third was a 48-year-old man. Each individual gave informed consent to participate, and a waiver was obtained from the North Dakota State University Institutional Review Board.

The participants collected each of the replicant samples between 7 am and 9 am on the same day. Following the instructions on the test kits, they rinsed their mouths with cool water, waited 5 minutes, and expectorated saliva directly into the collection tubes provided. This procedure was repeated for each sample. The women collected their samples on days 20 to 22 of their menstrual cycle, as detailed in the kit instructions.

The two women each provided three identically collected saliva samples to each lab. Samples were collected in a series, in the order shown in Table 1. The first sample for each laboratory was labeled as being from a 23-year-old menstruating woman who was taking oral contraceptives. The second sample was labeled as being from a 40-year-old premenopausal woman not on oral contraceptives. The third sample was labeled as being from a 50-year-old menopausal woman who was taking HRT. The second and third samples were submitted under fictitious names.

The man provided one sample to each laboratory. He labeled his samples as being from a 48-year-old perimenopausal woman not taking hormonal supplements and also submitted them under a fictitious female name.

We used fictitious names and demographics to blind the purpose of the study and to check that the laboratories reported actual hormone levels and not what would be expected for women having these demographic characteristics.

Since laboratory A's instructions stated that sugarless gum could be used to stimulate saliva production, participants chewed a new piece of gum for 5 minutes before collecting each sample for that laboratory. Laboratory B required its samples to be collected on two consecutive mornings and paired together for submission. This laboratory's instructions stated that chewing gum was not allowed, so gum was not used before collecting these samples. All samples were kept refrigerated until mailing. All samples were mailed at the same time—seven samples were sent to each laboratory—with requests for analysis of estradiol, progesterone, and testosterone.

Results

Laboratory A used an enzyme immunoassay and reported results in pg/mL, whereas laboratory B used a radioimmunoassay and reported results in pmol/L. We converted laboratory B's results to pg/mL to facilitate comparison of results.

Table 1 shows the "patient" description and results for each sample. There was striking variation in results within each laboratory for each participant. Within-subject coefficients of variation were 35% to 73% for estradiol, 8% to 103% for progesterone, and 13% to 40% for testosterone. Progesterone values differed by 6-fold for subject 2 in laboratory A. Laboratory B generally had a smaller variance in results, but the results were still less consistent than would be expected for the same patient. A wide variation was also evident between the two laboratories, with the mean reported estradiol level about three times higher in laboratory A than in B.

Although the two laboratories used different analytic methods, we expected similar results based on the reference ranges the laboratories provided. These ranges depended on patient demographics, but, for example, for the 23-year-old woman, the estradiol reference range was 1.0 pg/mL to 5.0 pg/mL in laboratory A and 1.5 pg/mL to 3.6 pg/mL in laboratory B. Times and dates on the laboratory reports mailed back to us indicated that laboratory A assayed the seven samples in three different batches over 24 hours, while laboratory B appeared to have run all seven samples at one time. Each laboratory claimed to have a normal between-assay coefficient of variation of 8% to 12% (personal communication with laboratory directors, May 28, 2003).

Discussion

Compounding pharmacists need to know how reliable saliva assays are before they use the results to formulate HRT products

for patients. We were curious about the quality of assays that can be ordered over the Internet with perhaps minimal quality control. Laboratory A is commonly used by compounding pharmacies in our community, and Laboratory B was randomly chosen from among many sites on the Internet that advertise the availability of hormone saliva tests. Laboratory B is also frequently used by compounding pharmacies in the United States. Therefore, their performances should be no worse than those of other U.S. laboratories that do saliva analyses.

The variable results are not explained by order of collection, since results do not consistently go up or down from sample 1 to sample 3. The somewhat better results of laboratory B might be explained by the fact they were all done in a single batch, while laboratory A appeared to perform the assays in three batches.

We followed each laboratory's instructions for sample collection carefully. Chewing gum has been reported to interfere with radioimmunoassay saliva hormone tests.[3] Laboratory B used radioimmunoassay, and its directions specifically advised against gum chewing. Laboratory A, however, used enzyme immunoassay and specifically suggested that chewing gum may be helpful for producing adequate saliva samples. We found no information that gum chewing would interfere with enzyme immunoassay.

Potential difficulties with saliva testing of hormones are well known. Saliva hormone concentrations are quite low and difficult to measure accurately. Contamination by blood will falsely elevate hormone levels,[4] and correlations between saliva and blood levels of hormones are often quite poor.[3] Radioimmunoassay results are difficult to standardize, and the literature offers scant guidance regarding how to collect saliva to maximize the reliability and validity of hormone results.[3] Dabbs et al.[2] evaluated the reliability of salivary testosterone assays in nine different laboratories. Each laboratory used its own radioimmunoassay procedures to analyze samples from a set of 100 men and 100 women. The mean correlation between pairs of laboratories was only $r = 0.44$ for men and $r = 0.46$ for women. Read[4] stated that the cases for measuring salivary testosterone and estradiol in women for the purpose of clinical decision making must still be considered unproven and that major differences in the levels reported do not correlate with any obvious differences in methodology.

The poor reliability of these laboratories has major clinical implications. For example, participant 3 was reported to be in the normal range for estradiol and below normal for progesterone in laboratory A, but in laboratory B was reported below normal for estradiol and in normal range for progesterone. Obviously, prescribed therapy for this "patient" would differ depending on which laboratory was used for evaluation.

Limitations

We collected saliva samples from only three participants and used only two laboratories. Thus, our results are not generalizable to other laboratories or types of patients. However, the very poor results suggest that potential problems exist with these types of assays. Also, we had no gold standard against which to evaluate the true value of any the results. However, our goal was to assess the reliability of the laboratories, not the accuracy of the tests.

Conclusion

Our findings suggest that laboratory values for saliva hormone samples collected with at-home test kits are not reliable. The individualization of HRT for patients is impossible without a reliable analysis. We suggest that compounding pharmacists periodically send in replicates of their own samples to test the reliability of the laboratories that they use.

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