IN VIVO EFFECT OF CLARITHROMYCIN ON MULTIPLE CYTOCHROME P450S

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ABSTRACT:

The in vivo effects of oral clarithromycin administration on the in vivo activity of cytochrome P450 1A2, 2C9, and 2D6 were determined. The cytochrome P450 probes caffeine (CYP1A2), tolbutamide (CYP2C9), and dextromethorphan (CYP2D6) were administered as an oral cocktail prior to and 7 days after oral clarithromycin (500 mg twice daily) administration to 12 healthy male subjects. Blood and urine samples were collected and assayed for each of the compounds and their metabolites using high-performance liquid chromatography. The CYP1A2 indices, oral caffeine clearance (6.2 ± 3.3 l/h before and 5.7 ± 4.2 l/h after, p > 0.05) and the 6-h paraxanthine to caffeine serum concentration ratio (0.49 ± 0.3 before and 0.44 ± 0.3 after, p > 0.05), were unchanged following clarithromycin dosing. Neither the tolbutamide oral clearance (0.77 ± 0.28 l/h before and 0.72 ± 0.24 l/h after, p > 0.05) nor the tolbutamide urinary metabolic ratio (779 ± 294 before and 681 ± 416 after, p > 0.05) indices of CYP2C9 were altered by clarithromycin administration. In the case of CYP2D6, the dextromethorphan to dextrorphan urinary ratio was not significantly different before (0.021 ± 0.04) and after (0.024 ± 0.06) clarithromycin dosing. In conclusion, clarithromycin does not appear to alter the in vivo catalytic activity of CYP1A2, CYP2C9, and CYP2D6 in healthy individuals as assessed by caffeine, tolbutamide, and dextromethorphan, respectively.

Clarithromycin is a macrolide antibiotic, which is widely used for the treatment of a myriad of infections such as those caused by Hemophilus influenzae, Mycobacterium avium, and Helicobacter pylori. Clarithromycin is oxidatively metabolized to 14-(R)-hydroxyclarithromycin or N-demethylated to N-desmethylclarithromycin and members of the CYP3A subfamily mediate these reactions (Rodrigues et al., 1997). Like erythromycin, clarithromycin is a potent mechanism-based inhibitor of CYP3A (Rodrigues et al., 1997). Clarithromycin reduces the clearance of a number of well characterized CYP3A substrates such as midazolam, cyclosporine, carbamazepine, and terfenadine (Albani et al., 1993; Honig et al., 1994; Jurima-Romet et al., 1994; Sketris et al., 1996; Gorski et al., 1998). For example, coadministration of clarithromycin with midazolam results in a 3-fold increase in midazolam results in a 3-fold increase in midazolam AUC (Gorski et al., 1998). Likewise, the systemic clearance of midazolam is reduced by 50% and the elimination half-life is increased 3- to 4-fold (Gorski et al., 1998).

While the effects of clarithromycin on CYP3A activity have been well defined, effects on other CYP families have not been as well characterized. For example, the macrolide antibiotics erythromycin and clarithromycin impair theophylline metabolism (Weinerberger et al., 1977; Periti et al., 1992; Gillum et al., 1993; Abbott Laboratories, 2000). It is clear that theophylline is primarily metabolized by CYP1A2 (Robson et al., 1988; Ha et al., 1995). Although there is some evidence to suggest that the 8-hydroxylation of theophylline is partly catalyzed by CYP3A, it is considered a minor and clinically insignificant pathway of theophylline oxidation (Robson et al., 1988; Tjia et al., 1996). However, the concomitant administration of theophylline and clarithromycin (macrolide antibiotics) is cautioned against in the package insert (Abbott Laboratories, 2000).

Clarithromycin has also been shown to alter the metabolism of pimozide and clozapine, which are substrates of CYP1A2 and CYP3A (Pirmohamed et al., 1995; Linnet and Olesen, 1997; Desta et al., 1998; Flockhart et al., 2000). In addition, there is some evidence to suggest that CYP2D6 may contribute to the metabolism of clozapine (Fischer et al., 1992). The role of CYP2D6 in the disposition of pimozide is unclear. Desta et al. (1999) noted that the plasma concentrations of pimozide tended to be higher in CYP2D6 poor metabolizers compared with CYP2D6 extensive metabolizers but this difference was not significant. However, pimozide is a potent inhibitor of this enzyme (Desta et al., 1998). Additionally, there have been reports of an interaction between clarithromycin and the CYP2C9 substrate warfarin, resulting in enhanced anticoagulation (Recker and Kier, 1997; Oberg, 1998; Gooderham et al., 1999).

The interactions between clarithromycin and substrates of CYP1A2, CYP2C9, and CYP2D6 suggest that in addition to CYP3A, clarithromycin may have inhibitory effects on other P450 enzymes. Thus, it is unclear whether clarithromycin alters the catalytic activity of other human CYPs in vivo. If clarithromycin affected other human P450s in addition to CYP3A, there would be a risk of additional unidentified drug-drug interactions. The goal of this study is to determine the in vivo effects of clarithromycin on multiple CYPs by using a drug cocktail consisting of caffeine, tolbutamide, and dextromethorphan.
Materials and Methods

Chemicals. Acetaminophen, chlorthalidone, codeine, dextromethorphan, ethylmorphine, and β-glucuronidase were purchased from Sigma Chemical Co. (St. Louis, MO). Acetoni-trile, methanol, isopropanol, chloroform, and tetrahydrofuran were purchased from Fisher Scientific (Pittsburgh, PA). 4-Hydroxytolbutamide and carboxytolbutamide were purchased from RBI/Sigma (Natick, MA) and GENTEST (Woburn, MA), respectively. Caffeine, paraxanthine, theobromine, theophylline, 8-hydroxycaffeine, dextromethorphan, 3-methoxyxymorphan, and 3-hydroxymorphinan were purchased from RBI/Sigma. Other chemicals were of the highest grade commercially available.

Cocktail Validation Study Design. After Institutional Review Board approval, participants provided written consent to take part in the study. Fifteen (eight females and seven males) healthy, nonsmoking volunteers age 29 ± 6 years and weighing 75 ± 19 kg participated in the four-way randomized, crossover study. The four arms of the study were the oral administration of 1) caffeine (Vivarin, 200 mg; SmithKline Beecham, Pittsburgh, PA); 2) tolbutamide (500 mg, Orinase; Pharmacia and Upjohn, Bridgewater, NJ); 3) dextromethorphan HBr (30 mg, Robitussin; Whitehall-Robbins, Madison, NJ); and 4) caffeine, tolbutamide, and dextromethorphan simultaneously as a cocktail. Fourteen of the volunteers were determined to have an extensive metabolizer CYP2D6 phenotype using the dextromethorphan to dextrorphan urinary metabolic ratio. Volunteers with a dextromethorphan to dextrorphan urinary metabolic ratio greater than or equal to 0.3 (i.e., poor metabolizers) were excluded from participating in this study (Kupfer et al., 1984). 2) Blood samples were obtained through an indwelling catheter located in the volunteer’s forearm at the following times: 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 24, 48, 72, and 96 h post tolbutamide and cocktail administration. When caffeine and dextromethorphan were administered separately, blood samples were obtained as described for 24 h. Urine was collected in 12-h intervals for 96 h following tolbutamide and cocktail administration. When dextromethorphan or caffeine was administered separately, urine was collected in 12-h intervals for 72 and 24 h, respectively. A minimum of 5 days and a maximum of 10 days separated each arm of the study. Serum and urine were stored at −20°C until analysis.

Clarithromycin P450 Study Design. Twelve healthy, nonsmoking, nonethanol drinking, male volunteers age 31 ± 9 years weighing 85 ± 13 kg participated in the study. The clarithromycin interaction study was conducted in an identical manner to the cocktail validation study except for the following:

1) Prior to inclusion in the study, the CYP2D6 phenotype was determined using the dextromethorphan to dextrorphan urinary metabolic ratio. Volunteers with a dextromethorphan to dextrorphan urinary metabolic ratio greater than or equal to 0.3 (i.e., poor metabolizers) were excluded from participating in this study (Kupfer et al., 1984). 2) Blood samples were obtained through an indwelling catheter located in the volunteer’s forearm at the following times: 1, 2, 6, 12, 24, 48, 72, and 96 h after dosing.

A fixed order design was used because the duration of any effect of clarithromycin on CYPs is unknown. One week after initial cocktail dosing, subjects began a 10-day regimen of 500 mg of clarithromycin (Biaxin; Abbott Laboratories, North Chicago, IL) twice daily. On day 7 of clarithromycin administration the volunteers adhered to a diet without caffeine or xanthine-related compounds (e.g., coffee, tea, cola, chocolate); citrus fruits and juices; and cruciferous vegetables such as mustard greens, broccoli, kale, and watercress; and foods cooked over charcoal. After an overnight fast, subjects reported to the General Clinical Research Center and were admitted. Subsequently, baseline serum and urine samples were obtained. The volunteers received either the cocktail of CYP probes (caffeine, tolbutamide, and dextromethorphan) or one of the components of the cocktail at 240 ml of distilled water orally. Blood samples (7 ml) were obtained through an indwelling catheter located in the volunteer’s forearm at the following times: 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 24, 48, 72, and 96 h post tolbutamide and cocktail administration. When caffeine and dextromethorphan were administered separately, blood samples were obtained as described for 24 h. Urine was collected in 12-h intervals for 96 h following tolbutamide and cocktail administration. When dextromethorphan or caffeine was administered separately, urine was collected in 12-h intervals for 72 and 24 h, respectively. A minimum of 5 days and a maximum of 10 days separated each arm of the study. Serum and urine were stored at −20°C until analysis.

Caffeine and Paraxanthine. Serum caffeine and paraxanthine concentrations were determined using high-performance liquid chromatography with a modified version of a previously published method (Grant et al., 1983; Gorski et al., 2000). The assay was used to routinely measure caffeine and paraxanthine concentrations between 0.3 and 20 μg/ml. Duplicate quality control samples were evaluated with each batch of samples. Analytical results were considered acceptable if quality control samples were within ±15% of the nominal value. Interday precision values were 7, 3, and 6% for caffeine and 3, 2, and 2%, for paraxanthine concentrations of 0.7, 1.4, and 16 μg/ml, respectively.

Tolbutamide and Metabolites. Tolbutamide, carboxytolbutamide, and 4-hydroxytolbutamide urine concentrations were determined using high-performance liquid chromatography using a modified version of a previously published method (Knoedel et al., 1987; Gorski et al., 2000). Duplicate quality control samples were assessed with each batch of samples and considered acceptable if the determined value was within ±15% of the expected value. The interday precision for carboxytolbutamide and 4-hydroxytolbutamide at 2.8 μg/ml was 4.5 and 7%, respectively. The interday accuracy at 2.8 μg/ml for carboxytolbutamide and 4-hydroxytolbutamide was 1 and 1%, respectively. For tolbutamide concentrations of 0.1, 0.4, 1.0, and 4.0 μg/ml, the interday precision was 8, 10, 12, and 13%, respectively, and the interday accuracy was 1, 8, 7, and 8%, respectively.

FIG. 1. Effect of probe drug coadministration on caffeine oral clearance (A), tolbutamide oral clearance (B), and urinary dextromethorphan to dextrorphan metabolic ratio (C), which are in vivo indices of CYP1A2, CYP2C9, and CYP2D6 activity, respectively.

The open and closed symbols represent the results for each of the volunteers. The solid diamonds represents the mean (±S.D.) for 15 individuals following probe drug administration alone or as a cocktail. In C the solid diamond represents the mean (±S.D.) for 14 CYP2D6 extensive metabolizers.

The accuracy values were 3, 1, and 1% for caffeine and 1, 2, and 1% for paraxanthine concentrations of 0.7, 1.4, and 16 μg/ml, respectively.

Tobutamide and Metabolites. Tolbutamide, carboxytolbutamide, and 4-hydroxytolbutamide urine concentrations were determined using high-performance liquid chromatography using a modified version of a previously published method (Knoedel et al., 1987; Gorski et al., 2000). Duplicate quality control samples were assessed with each batch of samples and considered acceptable if the determined value was within ±15% of the expected value.
To determine the oral clearance of tolbutamide, the 72-h cumulative caffeine was used. Others have demonstrated that the 6-h serum paraxanthine to caffeine concentration ratio was not significantly different following administration of tolbutamide alone and in combination with caffeine and dextromethorphan, respectively. One volunteer had a 6-fold lower tolbutamide oral clearance (0.15–0.21) compared with the other volunteers (0.96–1.03 l/h). Likewise, the elimination half-life was substantially greater (57 h) than the mean half-life determined for the other volunteers (8.4±1.8 h). It appears that this individual is a poor metabolizer of CYP2C9, however this has not been confirmed by genotyping.

**Results**

Fifteen (eight females, seven males; 14 extensive metabolizers, one poor metabolizer of CYP2D6) volunteers completed the cocktail validation portion of the study. The mean (±S.D.) caffeine serum concentrations are presented in Fig. 1A. No significant difference in the oral clearance of caffeine administered alone or as a component of the cocktail was observed (Fig. 1; Table 1). Likewise, the paraxanthine to caffeine serum concentration ratio was not significantly different (p>0.05, n=14) following the oral dosing of caffeine alone or together with dextromethorphan and tolbutamide.

The terminal elimination rate constant (k) was calculated using the slope of the log-linear regression of the terminal elimination phase. Area under the concentration time curve was calculated using the log-linear extrapolation to infinity using AUC∞. The mean (±S.D.) caffeine serum concentration ratio was not significantly different following administration of tolbutamide alone and in combination with caffeine and dextromethorphan, respectively. One volunteer had a 6-fold lower tolbutamide oral clearance (0.15–0.21) compared with the other volunteers (0.96–1.03 l/h). Likewise, the elimination half-life was substantially greater (57 h) than the mean half-life determined for the other volunteers (8.4±1.8 h). It appears that this individual is a poor metabolizer of CYP2C9, however this has not been confirmed by genotyping.

### Statistical Analysis

The difference between control and clarithromycin-treated group parameters was determined using a paired t test. The statistical analysis was performed using the computer program The SAS System for Windows (version 6.12; SAS Institute Inc., Cary, NC). A significance level of p≤0.05 was used. Assuming 80% power and an α level of 0.05, a sample size of 12 was sufficient to observe a 20% change in caffeine clearance, 6-h serum paraxanthine to caffeine concentration ratio, and the oral clearance of tolbutamide. In the case of the urinary dextromethorphan to dextrophan metabolic ratio a sample size of 12 was sufficient to detect a 100% change.

### In vivo indices of cytochrome P450 activity following administration of probe drugs alone and as a cocktail in 15 healthy volunteers

<table>
<thead>
<tr>
<th></th>
<th>Alone</th>
<th>Cocktail</th>
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<tr>
<td><strong>CYP1A2</strong></td>
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<tr>
<td>Oral caffeine clearance (l/h) (n=15)</td>
<td>5.0±1.8</td>
<td>5.4±2.8</td>
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<tr>
<td>Serum (6-h) paraxanthine/caffeine concentration ratio (n=14)</td>
<td>0.42±0.15</td>
<td>0.44±0.19</td>
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<tr>
<td><strong>CYP2C9</strong></td>
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<tr>
<td>Extensive metabolizer (n=14)</td>
<td></td>
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<tr>
<td>Oral tolbutamide clearance (l/h)</td>
<td>0.96±0.26</td>
<td>1.03±0.25</td>
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<tr>
<td>Urinary tolbutamide metabolic ratio</td>
<td>630±215</td>
<td>678±238</td>
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<tr>
<td>Poor metabolizer (n=1)</td>
<td></td>
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<tr>
<td>Oral tolbutamide clearance (l/h)</td>
<td>0.15</td>
<td>0.21</td>
</tr>
<tr>
<td>Urinary tolbutamide metabolic ratio</td>
<td>45</td>
<td>96</td>
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<tr>
<td><strong>CYP2D6</strong></td>
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<tr>
<td>Extensive metabolizer (n=14)</td>
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<tr>
<td>Urinary dextromethorphan/dextrorphan metabolic ratio</td>
<td>0.066±0.089</td>
<td>0.056±0.063</td>
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<tr>
<td>Poor metabolizer (n=1)</td>
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<tr>
<td>Urinary dextromethorphan/dextrorphan metabolic ratio</td>
<td>3.2</td>
<td>3.4</td>
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was observed (Fig. 3A). Likewise, a correlation between the 6-h paraxanthine/caffeine ratio and paraxanthine AUC/caffeine AUC ratio was observed (data not shown; \( n = 24, r = 0.93, p < 0.05 \)).

The in vivo activity of CYP2C9 was assessed by the urinary tolbutamide metabolic ratio and the oral clearance of tolbutamide (Fig. 2; Table 2). The urinary metabolic ratio decreased 13% from 860 ± 330 to 750 ± 460 but this change was not significant \( p > 0.05 \), Table 2). The oral clearance of tolbutamide was not significantly different before \( 0.77 ± 0.28 \) l/h and after \( 0.72 ± 0.24 \) l/h clarithromycin administration. Surprisingly, the oral clearance of tolbutamide was not highly correlated with the tolbutamide urinary ratio (Fig. 3B). CYP2D6 activity was determined using the 24-h dextromethorphan/dextrorphan urinary ratio, which was also unchanged after clarithromycin administration, \( 0.019 ± 0.039 \) before and \( 0.027 ± 0.063 \) after \( p = 0.29 \) (Fig. 2; Table 2).

**Discussion**

The current study was designed to evaluate whether clarithromycin altered the in vivo activity of CYP1A2, CYP2C9, and CYP2D6 in addition to its established effects on CYP3A4. These four enzymes are the principle drug-metabolizing enzymes in humans and account for the metabolism of >90% of administered drugs that require biotransformation for elimination. Each of the probe drugs used, tolbutamide, caffeine, and dextromethorphan, have been validated individually as effective and specific probes for CYP1A2, CYP2C9, and CYP2D6, respectively.

It is clear that macrolide antibiotics such as troleandomycin, erythromycin, and clarithromycin are potent irreversible inhibitors of CYP3A-mediated biotransformations both in vitro and in vivo. We have previously demonstrated that clarithromycin significantly inhibits CYP3A activity in vivo (Gorski et al., 1998). In that study, we used intravenous midazolam, and an oral solution of the stable isotope \( ^{15} \text{N}_3 \)-midazolam was administered simultaneously both before and after 7 days of clarithromycin to 16 healthy individuals. Systemic clearance decreased significantly from 29 to 10 l/h, suggesting an inhibition of hepatic CYP3A by clarithromycin (Gorski et al., 1998). However, oral bioavailability increased 2.5-fold after clarithromycin administration \( F = 0.31 ± 0.1 \) prior to treatment, \( F = 0.75 ± 0.02 \) after treatment \( p < 0.05 \). This increase in bioavailability could not be accounted for entirely by effects on hepatic metabolism and indicates that clarithromycin also inhibits gut wall metabolism. Thus, from these human data, 7 days of clarithromycin has substantially reduced CYP3A activity in the gastrointestinal epithelium and liver.

It is well established that CYP1A2 plays a prominent role in the \( N \)-demethylation of theophylline and that the 8-hydroxylation of theophylline is catalyzed by both CYP2E1 and CYP1A2 (Robson et al., 1988). In agreement with the in vitro data, the clearance of theophylline is increased by concurrent smoking and decreased following coadministration of known CYP1A2 inhibitors such as fluvoxamine and ciprofloxacin (Rasmussen et al., 1997). However, it is also clear that other agents such as the macrolide antibiotics, known inhibitors of CYP3A, and rifampin, a known CYP3A inducer, alter the clearance of theophylline in vivo (Adebayo et al., 1989; Upton, 1991a,b; Periti et al., 1992). For instance, coadministration of theophylline with troleandomycin results in a 50% reduction in the systemic clearance of theophylline and a corresponding 2-fold increase in the AUC (Weinberger et al., 1977). However, the ability of erythromycin to alter the disposition of theophylline is not as clear with numerous reports supporting and refuting an interaction between theophylline and erythromycin (Upton, 1991a,b). Others have indicated that clarithromycin impairs the metabolism of theophylline and enhances the anticoagulant properties of warfarin in vivo (Recker and Kier, 1997; Oberg, 1998; Gooderham et al., 1999; Abbott Laboratories, 2000). This raises the question as to whether clarithromycin and macrolide antibiotics in general might have broader inhibitory capabilities in humans. Due to the potential for theophylline toxicity, we examined the potential for clarithromycin to alter the in vivo CYP1A2 activity using the well characterized CYP1A2 probe caffeine.

In contrast to the observations of others, clarithromycin failed to alter the in vivo CYP1A2 activity as assessed by the disposition of caffeine. Similarly, Rasmussen et al. (1997) reported a poor correlation between the 6-h paraxanthine to caffeine plasma ratio and caffeine urinary metabolic ratio and the oral clearance of theophylline and the partial theophylline metabolite clearances in vivo. Taken
Disposition of theophylline. Alternatively, troleandomycin and clarithromycin may inhibit the CYP2E1-mediated metabolism of theophylline, but there is little data to support this line of reasoning.

The use of the cocktail of probes allowed data to be collected for three separate enzyme systems, simultaneously. In addition to limiting individual differences, a cocktail of probes also enables one to study a large number of enzymes in a shorter duration of time. Frye et al. (1997) administered a five-drug cocktail, the "Pittsburgh cocktail," verifying that multiple probe drugs could be administered together without significant metabolic interactions. However, the utility of the Pittsburgh cocktail is limited because 1) one of the probes used, debisouquine, is not available for use in the United States; 2) there is no CYP2C9 probe, which is a major drug-metabolizing P450 enzyme; 3) dapsone is used as an index of CYP3A activity; and 4) a limitation of the Pittsburgh cocktail approach is that urinary ratios for caffeine are used as a marker for CYP1A2. Typically, urinary ratios do not correlate with serum AUC for caffeine. Our approach uses three readily available and generally inert drugs, namely, caffeine, tolbutamide, and dextromethorphan and all are simple to administer and have been previously validated as probes individually.

In conclusion, we have verified that there is no interaction between caffeine, tolbutamide, and dextromethorphan when coadministered. Additionally, a good correlation was observed between the 6-h serum paraxanthine to caffeine ratio and the serum caffeine AUC, oral caffeine clearance, and the paraxanthine to caffeine area under the concentration time curve ratio, indicating that using a single time point to measure enzyme activity simplifies and could potentially shorten the duration of drug interaction and metabolism studies while limiting the amount of blood obtained from the individual. Finally, we found that clarithromycin had no significant effect on the catalytic activities of CYP1A2, CYP2C9, and CYP2D6 as assessed by caffeine, tolbutamide, and dextromethorphan when coadministered. However, the utility of the Pittsburgh cocktail approach is limited because 1) one of the probes used, debisouquine, is not available for use in the United States; 2) there is no CYP2C9 probe, which is a major drug-metabolizing P450 enzyme; 3) dapsone is used as an index of CYP3A activity; and 4) a limitation of the Pittsburgh cocktail approach is that urinary ratios for caffeine are used as a marker for CYP1A2. Typically, urinary ratios do not correlate with serum AUC for caffeine. Our approach uses three readily available and generally inert drugs, namely, caffeine, tolbutamide, and dextromethorphan and all are simple to administer and have been previously validated as probes individually.

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