OBSTETRICS

Quality assessment of compounded 17-hydroxyprogesterone caproate

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OBJECTIVE: The purpose of this study was to evaluate the quality of compounded 17-hydroxyprogesterone caproate (17-OHPC).

STUDY DESIGN: Compounded 17-OHPC that was obtained from 15 compounding pharmacies throughout the United States was analyzed for potency, impurities, sterility, and pyrogen status.

RESULTS: Eighteen samples were supplied by 15 compounding pharmacies. The concentration of 17-OHPC in all samples was within the specification limits, and all tested samples passed sterility and pyrogen testing. Only 1 of 18 samples was out of specification limits for impurities.

CONCLUSION: Compounded 17-OHPC that was obtained from 15 pharmacies throughout the United States did not raise safety concerns when assessed for potency, sterility, pyrogen status, or impurities.

Key words: compounded 17-OHPC, impurity analysis, potency, sterility and pyrogen status

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The use of 17-alpha-hydroxyprogesterone caproate (17-OHPC) reduces the risk of recurrent spontaneous preterm birth in women with singleton gestation and a previous preterm birth.[1] Until recently this medication was available only from independent compounding pharmacies across the country. In February 2011, the Food and Drug Administration (FDA) approved the New Drug Application (NDA) of KV Pharmaceuticals to market 17-OHPC as Makena (Ther-Rx Corporation, St. Louis, MO).[2] The company initially

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set the price of Makena at $1500/ injection, whereas the cost of compounded 17-OHPC before FDA approval was $10-15/ injection. The resultant public outcry led to congressional hearings and universal condemnation of the company's pricing policies.[3-5] Consequently, the FDA issued a statement indicating it would not take enforcement action against compounding pharmacies that continued to produce 17-OHPC to allow continued patient access to this medication.[6]

A recent report by Chollet and Jozwiakowski[7] from the Ther-Rx Corporation (markets Makena) suggested that compounded 17-OHPC poses a risk because many unspecified impurities were identified in the active pharmaceutical ingredients that were used to compound 17-OHPC and that the concentration of the compounded product was commonly not in the range of accepted potency. The FDA conducted their own investigation and could not identify any major safety problems for compounded 17-OHPC. The FDA, however, stated that it was again applying its normal enforcement policy to compounded 17-OHPC.[8]

We undertook this study after the report of Chollet and Jozwiakowski[7] and before the time the FDA undertook their investigation.[8] Our purpose was to obtain compounded 17-OHPC formulations from compounding pharmacies throughout the United States and to analyze the product for potency (concentration), impurities, sterility, and pyrogen status. Sterility and pyrogen status assessments of compounded 17-OHPC were not provided in the reports of the FDA[8] or of Chollet and Jozwiakowski.[7] Additionally, several differences in the

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TABLE 1
Chemical analysis of 17-OHPC, benzyl benzoate, and benzyl alcohol from different compounding pharmacies

Sample	17-OHPC, mg/mL	Percentage of labeled concentration, %	Content of benzyl benzoate, %	Content of benzyl alcohol, %
1	239	96	49	2.2
2	253	101	46	2.0
3	261	104	47	2.3
4	260	104	48	1.9
5	251	100	51	2.1
6	244	98	46	2.8
7	244	98	43	2.1
8	255	102	44	2.6
9	254	102	44	1.9
10	247	99	46	1.9
11	265	106	48	2.3
12	265	106	49	2.1
13	251	100	47	2.0
14	247	99	48	1.7
15	248	99	48	1.9
16	243	97	49	2.0
17	243	97	46	2.0
18	243	97	45	2.1
Mean ± SD	251 ± 8 (CV, 3)	100 ± 3 (CV, 3)	47 ± 2 (CV, 4)	2.1 ± 0.3 (CV, 1)
90% CI	248–254	99–101	46–48	2.0–2.2
Accepted criteria[a]	225–275	90–110	46	1.7–2.3

CI, confidence interval; CV, coefficient of variation; *17-OHPC*, 17-hydroxyprogesterone caproate.

[a] Criteria in Makena (Ther-Rx Corporation, St. Louis, MO) New Drug Application.

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assessment of compounded 17-OHPC were evident in those 2 reports.

Materials and Methods

This study has been deemed to be exempt by the University of Pittsburgh institutional review board because it involves no patients or biologic materials.

Identification of compounding pharmacies for recruitment

Twenty Maternal-Fetal Medicine specialists who were practicing in high-volume clinical centers (eg, university hospital-based clinics or large group practices) were contacted to obtain information regarding the compounding pharmacies that were used to fill their patients' prescriptions of 17-OHPC. Many of these physicians were identified based on their participation as clinical investigators in various research networks.

Recruitment of the compounding pharmacies

Compounding pharmacists, who were contacted by study investigators or by the participating Maternal-Fetal Medicine clinicians, were asked to participate in the study. A representative sample of their compounded 17-OHPC was purchased and shipped to the University of Pittsburgh for testing. The funds for purchase of the compounded 17-OHPC came from the University of Pittsburgh at times that were not predictable. This uncertainty of time of purchase lessens the possibility that the pharmacies had any opportunity to provide anything other than a "representative sample" of 17-OHPC. Each pharmacist was then asked to participate in a brief survey regarding their compounding and quality assurance practices. The pharmacies' voluntary accreditation status with the Pharmacy Compounding Accreditation Board was assessed by reviewing the website of accredited pharmacies (www.pcab.org/accredited-pharmacies; accessed on June 21, 2013). Samples (n = 3) were also from a research pharmacy that was used by the Maternal-Fetal Medicine Units Network and the Obstetrical-Fetal Pharmacology Research Units Network in trials that used 17-OHPC.

Sample analysis

Compounded 17-OHPC that was obtained from these various compounding pharmacies was stored at room temperature until analysis for content uniformity, impurity analysis, microbiologic testing, and pyrogen status.

Content analysis

Content and impurity analysis were performed at the University of Pittsburgh with high-performance liquid chromatography (HPLC) with a Waters 2695 Separations Module attached to a Waters 2998 Photodiode Array Detector 9 (Waters Corporation, Milford, MA). Aliquots of the samples were removed from the container in a laminar flow hood at room temperature and were tested to evaluate, in triplicate, concentrations of 17-OHPC, benzyl alcohol (a preservative), and benzyl benzoate (used to enhance solubility of 17-OHPC in castor oil). The sample was diluted with methanol or acetonitrile to a final 17-OHPC concentration of 50 μg/mL. Twenty microliters of this final solution was injected onto the HPLC. The concentrations of 17-OHPC (wave length, 242 nm), benzyl alcohol (wave length, 206 nm), and benzyl benzoate (wave length, 229 nm) in each sample were quantified with the use of corresponding standard compounds. The